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	L #	Hits	Search Text
1	L1	9732	((435/4) or (435/6) or (435/7.1) or (435/40.5) or (424/9.1)).ccls.
2	L2	529	shepard$.in.
3	L3	1	1 and 2
4	L4	618498	extrachromosomal or (double minute) or (gene amplfication)
5	L5	8193	4 and 1
6	L6	276319	screen$4
7	L7	5287	6 and 5
8	L8	1067	hydroxyurea or guanozole or phosphonacetyl or aphidicolin or desferioxamine
9	L9	67	8 and 7
10	L10	69	micronuclei
11	L11	2	10 and 9
12	L12	10	10 and 7
13	L14	10	12 and 13
14	L13	11	10 and 5

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     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 12:51:39 ON 06 JUL 2000
L1          725 S ((WAHL G.M.) OR (WAHL G M) OR (WAHL, GEOFFREY M.) OR (WAHL,
G
L2         3480 S ((SHIMIZU N.) OR (SHIMIZU N) OR (SHIMIZU, NORIAKI) OR
(SHIMIZ
L3         1524 S ((KANDA T.) OR (KANDA T) OR (KANDA, TERU) OR (KANDA, T.))/AU
L4          253 S ((SHEPARD H.M.) OR (SHEPARD H M) OR (SHEPARD, H. MICHAEL) OR
L5            0 S L1 AND L2 AND L3 AND L4
L6         5644 S SHEPARD?/AU
L7            0 S L1 AND L2 AND L3 AND L6
L8        21567 S WAHL?/AU
L9        78655 S SHIMIZU?/AU
L10       13852 S KANDA?/AU
L11           0 S L6 AND L8 AND L9 AND L10
L12       12474 S MICRONUCLEI OR (INDUCTION OF MICRONUCLEI)
L13          25 S L12 AND (L1 OR L2 OR L3 OR L4)
L14          10 DUP REM L13 (15 DUPLICATES REMOVED)
L15      123043 S APHIDICOLIN OR DEFEROXAMINE OR GUANOZOLE OR HYDROXYUREA OR
PH
L16         117 S L15 AND L12
L17          59 DUP REM L16 (58 DUPLICATES REMOVED)
L18      277169 S (GENE AMPLIFICATION) OR EXTRACHROMOSOM? OR AMPLIFI?
L19         193 S L18 AND L12
L20     6822766 S SCREEN? OR TREAT?
L21          50 S L20 AND L19
L22          20 DUP REM L21 (30 DUPLICATES REMOVED)


L22  ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:         1999:454270  CAPLUS
DOCUMENT NUMBER:          131:82943
TITLE:                    Compositions and methods for identifying therapeutic
                          agents and for  ***treating***  cells having double
                          minute DNA
INVENTOR(S):              Wahl, Geoffrey M.; Shepard, H. Michael; Shimizu,
                          Noriaki
PATENT ASSIGNEE(S):       Newbiotics, Inc., USA; The Salk Institute; Kanda,
Teru
SOURCE:                   PCT Int. Appl., 80 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 9935292         A1   19990715       WO 1999-US601     19990111
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
             MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
             TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
        RW:  GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9922217         A1   19990726       AU 1999-22217     19990111
PRIORITY APPLN. INFO.:                     US 1998-71146     19980112
                                           US 1998-77644     19980311
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WO 1999-US601 19990111

OTHER SOURCE(S): MARPAT 131:82943

AB Methods are provided for ***screening*** test substances for their ability to inhibit, enhance, or eliminate double minute (DM) or ***extrachromosomal*** DNA by micronucleation in cells. Also provided is a method for inducing maturation or death of a cell having the capacity to generate ***micronuclei*** . The invention also provides a method of ***treating*** a disease in a subject, the cells correlated with the disease having DM and ***extrachromosomal*** DNA as well as the capacity to generate ***micronuclei*** to capture them. Further provided is a method of detecting chromosomal and ***extrachromosomal*** DNA in a cell.

REFERENCE COUNT: 5

REFERENCE(S):
(1) Eckhardt; Proc Natl Acad Sci USA 1994, V91, P6674 CAPLUS
(2) Kanda; Current Biology 1998, V8, P377 CAPLUS
(3) Shimizu; Nature Genetics 1996, V12, P65 CAPLUS
(4) Sullivan; Methods in Cell Biology 1999, V58, P203
(5) Von Hoff; Cancer Research 1991, V51, P6273 CAPLUS

L22 ANSWER 2 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:212333 BIOSIS

DOCUMENT NUMBER: PREV199900212333

TITLE: ***Micronuclei*** formation and aneuploidy induced by Vpr, an accessory gene of human immunodeficiency virus type 1.

AUTHOR(S): Shimura, Mari; Tanaka, Yoshikazu; Nakamura, Satoshi; Minemoto, Yuzuru; Yamashita, Katsumi; Hatake, Kiyohiko; Takaku, Fumimaro; Ishizaka, Yukihito (1)

CORPORATE SOURCE: (1) Department of Intractable Diseases, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo, 162-8655 Japan

SOURCE: FASEB Journal, (April, 1999) Vol. 13, No. 6, pp. 621-637. ISSN: 0892-6638.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Vpr, an accessory gene of HIV-1, induces cell cycle abnormality with accumulation at G2/M phase and increased ploidy. Since abnormality of mitotic checkpoint control provides a molecular basis of genomic instability, we studied the effects of Vpr on genetic integrity using a stable clone, named MIT-23, in which Vpr expression is controlled by the tetracycline-responsive promoter. ***Treatment*** of MIT-23 cells with doxycycline (DOX) induced Vpr expression with a giant multinuclear cell formation. Increased ***micronuclei*** (MIN) formation was also detected in these cells. Abolishment of Vpr expression by DOX removal induced numerous asynchronous cytokinesis in the multinuclear cells with leaving MIN in cytoplasm, suggesting that the transient Vpr expression could cause genetic unbalance. Consistent with this expectation, MIT-23 cells, originally pseudodiploid cells, became aneuploid after repeated expression of Vpr. Experiments using deletion mutants of Vpr revealed that the domain inducing MIN formation as well as multinucleation was located in the carboxy-terminal region of Vpr protein. These results suggest that

Vpr induces genomic instability, implicating the possible role in the development of AIDS-related malignancies.

L22 ANSWER 3 OF 20 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999234288 MEDLINE
DOCUMENT NUMBER: 99234288
TITLE: Co-localization of mitochondrial and double minute DNA in the nuclei of HL-60 cells but not normal cells.
AUTHOR: Hirano T; Shiraishi K; Adachi K; Miura S; Watanabe H; Utiyama H
CORPORATE SOURCE: Life Science Group, Faculty of Integrated Arts and Sciences, Hiroshima University, Kagamiyama 1-7-1, Higashihiroshima 739-8521, Japan.
SOURCE: MUTATION RESEARCH, (1999 Apr 6) 425 (2) 195-204. Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990705
AB In an attempt to isolate genes located on double minute (Dmin) DNA in HL-60 cells, we prepared DNA probe from purified ***micronuclei*** . Micronucleation was induced in HL-60 cells by ***treatment*** with hydroxyurea. ***Screening*** of a cDNA library unexpectedly produced a number of clones containing mitochondrial DNA (mtDNA) sequences. Here, we show that ***amplified*** mtDNA sequences were localized in nuclei and ***micronuclei*** of HL-60 and COLO 320DM cells, but not in nuclei of WI-38 normal human fibroblasts or peripheral blood T-cells. To unequivocally demonstrate the presence of mtDNA inside of nuclei and ***micronuclei*** , we obtained tomographic fluorescence in situ hybridization (FISH) images of mtDNA by confocal microscopy of consecutive sections of paraformaldehyde (PFA)-fixed material. We also located mtDNA in nuclear buds and purified ***micronuclei*** . Dmin DNA and mtDNA were always located at similar sites. The mechanisms of nuclear retention of mtDNA and Dmin DNA and the resulting influence on tumorigenesis are discussed. Copyright 1999 Elsevier Science B.V.

L22 ANSWER 4 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:248090 BIOSIS
DOCUMENT NUMBER: PREV199900248090
TITLE: Co-localization of mitochondrial and double minute DNA in the nuclei of HL-60 cells but not normal cells.
AUTHOR(S): Hirano, Tetsuo; Shiraishi, Kazunori; Adachi, Koichiro; Miura, Saori; Watanabe, Hiromi; Utiyama, Hiroyasu (1)
CORPORATE SOURCE: (1) Life Science Group, Faculty of Integrated Arts and Sciences, Hiroshima University, Kagamiyama 1-7-1, Higashihiroshima, 739-8521 Japan
SOURCE: Mutation Research, (April 6, 1999) Vol. 452, No. 2, pp. 195-204.
ISSN: 0027-5107.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In an attempt to isolate genes located on double minute (Dmin) DNA in HL-60 cells, we prepared DNA probe from purified ***micronuclei*** . Micronucleation was induced in HL-60 cells by ***treatment*** with

hydroxyurea. ***Screening*** of a cDNA library unexpectedly produced a number of clones containing mitochondrial DNA (mtDNA) sequences. Here, we show that ***amplified*** mtDNA sequences were localized in nuclei and ***micronuclei*** of HL-60 and COLO 320DM cells, but not in nuclei of WI-38 normal human fibroblasts or peripheral blood T-cells. To unequivocally demonstrate the presence of mtDNA inside of nuclei and ***micronuclei*** , we obtained tomographic fluorescence in situ hybridization (FISH) images of mtDNA by confocal microscopy of consecutive sections of paraformaldehyde (PFA)-fixed material. We also located mtDNA in nuclear buds and purified ***micronuclei*** . Dmin DNA and mtDNA were always located at similar sites. The mechanisms of nuclear retention of mtDNA and Dmin DNA and the resulting influence on tumorigenesis are discussed.

L22 ANSWER 5 OF 20 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999078042 MEDLINE
DOCUMENT NUMBER: 99078042
TITLE: Triethylene glycol dimethacrylate induces large deletions in the hprt gene of V79 cells.
AUTHOR: Schweikl H; Schmalz G
CORPORATE SOURCE: Department of Operative Dentistry and Periodontology, University of Regensburg, D-93042, Regensburg, Germany.. helmut.schweikl@klinik.uni-regensburg.de
SOURCE: MUTATION RESEARCH, (1999 Jan 2) 438 (1) 71-8. Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199905
ENTRY WEEK: 19990503
AB Acrylate esters are applied in industrial and consumer products often associated with polymers and resins. The difunctional methacrylate, triethylene glycol dimethacrylate (TEGDMA), is also frequently included in dental composite materials. Recently, mutagenicity testing of the compound revealed the induction of gene mutations at the hprt locus in V79 cell [H. Schweikl, G. Schmalz, K. Rackebrandt, The mutagenic activity of unpolymerized resin monomers in Salmonella typhimurium and V79 cells, Mutat. Res. 415 (1998) 119-130]. In the present study, TEGDMA caused a dose dependent increase of the number of ***micronuclei*** in V79 cells. Furthermore, the mutation spectra induced in exon sequences of the hprt gene in HPRT-deficient V79 cell clones were analyzed by the polymerase chain reaction (PCR). No DNA sequence deletions were observed in spontaneously occurring HPRT-deficient cell clones at the molecular level after PCR analysis, indicating that all spontaneous mutations were caused by point mutations. However, TEGDMA ***treated*** V79 cell cultures exhibited different mutation spectra. Only one cell clone among a total of 25 contained all exon sequences of the hprt gene. Large DNA sequences were deleted in 24 cell clones. Partial gene deletions occurred in four clones from exon 5 through 9, and exon 1 was not ***amplified*** in one cell clone. Exon sequences of the hprt gene were totally deleted in

19 HPRT-deficient clones. The induction of mostly large deletions in the genome of mammalian cells, like the mutation spectra induced by TEGDMA in V79 cells here, is probably typical for crosslinking agents, including anticancer drugs. Identical types of mutations including chromosomal aberrations and the formation of ***micronuclei*** in vitro were observed for acrylates and methacrylates tested so far in various mutation assays. Therefore, we conclude by analogy that the induction of large DNA sequence deletions as shown here with the reactive dimethacrylate, triethylene glycol dimethacrylate, is probably common for acrylates and methacrylates. Copyright 1999 Elsevier Science B.V.

L22 ANSWER 6 OF 20 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998400220 MEDLINE
DOCUMENT NUMBER: 98400220
TITLE: Fractionated ionizing radiation accelerates loss of ***amplified*** MDR1 genes harbored by ***extrachromosomal*** DNA in tumor cells.
AUTHOR: Sanchez A M; Barrett J T; Schoenlein P V
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta 30912, USA.
SOURCE: CANCER RESEARCH, (1998 Sep 1) 58 (17) 3845-54.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199811
ENTRY WEEK: 19981103

AB In tumor specimens such as those from neuroblastoma, ovarian, and lung carcinoma patients, the prevalence of ***extrachromosomal*** circular DNA molecules harboring ***amplified*** genes has been well established. In some cases, the ***amplified*** genes have been identified as oncogenes, and their increased expression appears to contribute to the maintenance and progression of the malignancy. The aim of this study was to investigate the effect of fractionated radiation ***treatment*** , given in daily doses similar to those administered clinically, on the stability of ***extrachromosomal*** circular DNA molecules in cancer cells. Our studies were conducted with multidrug-resistant KB cells, which harbor ***extrachromosomal*** copies of the multidrug resistance gene (MDR1) almost exclusively on circular DNA molecules of approximately 750 and 1500 kb pairs. This size range is representative of ***extrachromosomal*** circular DNA molecules that have been shown to harbor ***amplified*** oncogenes in vivo. Exponentially growing MDR KB cells were exposed to 1400 and 2800 cGy ionizing radiation administered in 7 and 14 fractions, respectively, at 200 cGy per fraction/day. A statistically significant decrease in MDR1 ***extrachromosomal*** gene copy number was reproducibly detected in the irradiated cells compared with unirradiated cells passaged for the duration of the experiment in the absence of radiation ***treatment*** . This decrease was accompanied by a reduction in multidrug resistance and in P-glycoprotein levels, as determined by clonogenic dose-response assays and Western analyses, respectively. P-glycoprotein is a multidrug transporter encoded by the MDR1 gene. Fluorescence in situ hybridization studies further determined that ***extrachromosomal*** circular DNA loss correlated to the entrapment of these DNA molecules in

radiation-induced ***micronuclei*** . These results indicate that radiation-induced loss of ***extrachromosomally*** ***amplified*** genes from tumor cells via their entrapment in ***micronuclei*** contributes to the improved therapeutic response observed for some cancers.

L22 ANSWER 7 OF 20 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:221832 BIOSIS
DOCUMENT NUMBER: PREV199800221832
TITLE: A simple and efficient method for microdissection and microFISH.
AUTHOR(S): Engelen, John J. M. (1); Albrechts, Jozefa C. M.; Hamers, Guus J. H.; Geraedts, Joep P. M.
CORPORATE SOURCE: (1) Dep. Mol. Cell Biol. Genet., Univ. Limburg, P.O. Box 616, 6200 MC Maastricht Netherlands
SOURCE: Journal of Medical Genetics, (April, 1998) Vol. 35, No. 4, pp. 265-268.
ISSN: 0022-2593.
DOCUMENT TYPE: Article
LANGUAGE: English
AB A simple and efficient method for the dissection of (marker) chromosomes, (micro)nuclei, and chromosome regions is presented. Before microdissection, metaphases are overlaid with milli-Q water to rehydrate the chromosomes, which makes them soft and sticky. The dissected chromosome fragments are dissolved without proteinase-K or topoisomerase ***treatment*** and directly ***amplified*** using a degenerate oligonucleotide primed polymerase chain reaction (DOP-PCR). The advantages of this microFISH method over previously reported methods are: (1) microdissection in this way is very fast; (2) a chromosome, marker, (micro)nucleus, or chromosome region is collected as a whole using only one microneedle; (3) the dissected material sticks tightly to the needle without the risk of getting lost; (4) no Sequenase is used in the DOP-PCR reaction which reduces the risk of contamination.

L22 ANSWER 8 OF 20 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998159829 MEDLINE
DOCUMENT NUMBER: 98159829
TITLE: In vivo protection by cimetidine against fast neutron-induced ***micronuclei*** in mouse bone marrow cells.
AUTHOR: Mozdarani H; Khoshbin-Khoshnazar A R
CORPORATE SOURCE: School of Medical Sciences, Tarbiat Modarres University, Tehran, Iran.
SOURCE: CANCER LETTERS, (1998 Feb 13) 124 (1) 65-71.
Journal code: CMX. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199805
ENTRY WEEK: 19980504
AB We have previously shown that cimetidine is capable of reducing the clastogenic effect of gamma-rays. In this research the radioprotective property of this drug was examined against low doses of fast neutrons using the micronucleus assay. Swiss albino male mice (12 weeks old) were irradiated by fast neutrons emitted from a 241Am-9Be source. The absorbed doses were 1.5, 2.25, 3.375 and 5.06 cGy at a dose rate of 0.718 cGy/h. Two hours prior to neutron irradiation mice were ***treated*** by cimetidine at a concentration of 15 mg/kg body weight injected i.p. Mice

were sacrificed by cervical dislocation at different post-irradiation times (24, 48 and 72 h). The results obtained show that the frequency of neutron-induced ***micronuclei*** in polychromatic erythrocytes (PCEs) is significantly higher than those of control groups ($P < 0.05$) at the neutron doses used in these experiments. Moreover, cimetidine effectively reduced (1.5-2-fold) the frequency of ***micronuclei*** in PCE ($P < 0.05$). These results show that cimetidine can protect bone marrow cells against clastogenic effects of low dose fast neutrons and hence high linear energy transfer (LET) radiation. The mechanism by which cimetidine reduces the clastogenic effects of fast neutrons is not fully understood. It might act through a free radical scavenging mechanism associated with the ***amplification*** of the glutathione system.

L22 ANSWER 9 OF 20 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999015649 MEDLINE
DOCUMENT NUMBER: 99015649
TITLE: Antigenotoxic effects of cimetidine against benzene induced ***micronuclei*** in mouse bone marrow erythrocytes.
AUTHOR: Mozdarani H; Kamali S
CORPORATE SOURCE: School of Medical Sciences, Tarbiat Modarres University, Tehran, Iran.
SOURCE: TOXICOLOGY LETTERS, (1998 Sep 30) 99 (1) 53-61.
Journal code: VXN. ISSN: 0378-4274.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199906
ENTRY WEEK: 19990603
AB An in vivo micronucleus assay using Balb/C male mice was used to examine antigenotoxic effects of cimetidine (CM) on benzene (BZN) induced genotoxic effects. CM not only has therapeutic and immunomudolatory role, but it has also been shown to protect bone marrow stem cells from radiation induced clastogenic effects. Therefore, in the present study we attempt to investigate the protective effects and possible mechanisms involved in the effects of CM. An 8-week-old male Balb/C mice (22+/-4 g weight) were ***treated*** with different doses of BZN (400, 600 and 800 mg/kg body weight), i.p. and sampled at 24, 48 and 72 h after ***treatment*** by cervical dislocation. Various doses of CM (10, 15, 30 mg/kg) were used in association with BZN and 1-2 h prior to BZN ***treatment*** . Results show that BZN effectively induced ***micronuclei*** in polychromatic erythrocytes (PCEs). Application of CM led to a significant reduction of ***micronuclei*** in PCEs, i.e. 2-fold after 10 mg/kg and 3-fold after 30 mg/kg CM ***treatment*** . Results also indicate CM was more effective when used in combination with BZN. Therefore, results indicate that CM could reduce clastogenic effects of BZN. Although further investigations are needed to reveal the mechanistical background behind the effect, the most probable mechanism involved might be free radical scavenging. This mechanism might be associated with ***amplification*** of glutathione system and cytochrome P-450 inhibition.

L22 ANSWER 10 OF 20 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97209925 MEDLINE
DOCUMENT NUMBER: 97209925
TITLE: Involvement of calcium-dependent protein kinase C in

arsenite-induced genotoxicity in Chinese hamster ovary cells.
AUTHOR: Liu Y C; Huang H
CORPORATE SOURCE: Institute of Radiation Biology, National Tsing-Hua University, Hsinchu, Taiwan, Republic of China.
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1997 Mar 1) 64 (3) 423-33.
Journal code: HNF. ISSN: 0730-2312.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707

AB Arsenic is the first metal to be identified as a human carcinogen. Arsenite, one inorganic form of arsenic, has been found to induce sister chromatid exchange, chromosome aberrations, and ***gene*** ***amplification*** in a variety of in vitro systems. In this study of arsenite-induced genotoxicity represented a ***micronuclei*** production in Chinese hamster ovary cells (CHO-K1), we found that the calcium channel blocker, verapamil, can potentiate arsenite-induced ***micronuclei*** . And after arsenite ***treatment*** , the elevation of intracellular calcium was observed. When extracellular calcium was depleted during arsenite ***treatment*** , the arsenite-induced ***micronuclei*** formation was significantly suppressed. These data indicated that a calcium ion plays an essential role in arsenite-induced genotoxicity. Further, it was found that the cotreatment of arsenite and a calcium ionophore, A23187, can increase the ***micronuclei*** induction. In contrast, pretreatment of the intracellular calcium chelator, quin 2, significantly inhibited ***micronuclei*** production of arsenite administration. In addition, we measured the activity of calcium- and phospholipid-dependent protein kinase C (PKC) and found that arsenite can activate PKC activity in a dose-dependent manner. Subsequently, some PKC activators and inhibitors were applied to investigate the involvement of PKC on arsenite-induced ***micronuclei*** formation. It was found that H7, a PKC inhibitor, can depress but TPA, a PKC activator, can enhance arsenite-induced ***micronuclei*** significantly. These data indicated that arsenite exposure perturbs intracellular calcium homeostasis and activates PKC activity. As a result, the activation of PKC activity may play an important role in arsenite-induced genotoxicity.

L22 ANSWER 11 OF 20 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97033561 MEDLINE
DOCUMENT NUMBER: 97033561
TITLE: Cell-cycle arrest, micronucleus formation, and cell death in growth inhibition of MCF-7 breast cancer cells by tamoxifen and cisplatin.
AUTHOR: Otto A M; Paddenberg R; Schubert S; Mannherz H G
CORPORATE SOURCE: Institut fur Pharmazie, Universitat Regensburg, Germany.
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1996) 122 (10) 603-12.
Journal code: HL5. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199701
ENTRY WEEK: 19970104

AB The induction of cell death along with cell-cycle arrest is one of the foremost mechanisms regulating cell growth. In the human breast carcinoma cell line MCF-7 we investigated two chemotherapeutic agents, the antiestrogen tamoxifen and the DNA-damaging drug cisplatin, for the relative contribution of these mechanisms to growth inhibition in culture.

Growth kinetics and flow cytometry confirmed that tamoxifen at 1 microM acts mainly by arresting cells in the G0/G1 phase of the cell cycle. Compared to untreated controls, only a few more cells were detached from the monolayer and dead after a 5-day incubation. On the other hand, cisplatin at 1 microM did not induce the well-defined G2/M-arrest reported for other cell types, but resulted in a marked increase in the rate of cell death. A morphological feature observed, especially with cisplatin- ***treated*** MCF-7 cells, was the formation of numerous ***micronuclei*** (in up to 30% of the cells) and an increase in the number of binucleate cells (up to 20%). In both tamoxifen- and cisplatin- ***treated*** cultures, cell death appeared to occur by apoptosis, as indicated morphologically by cellular and nuclear shrinkage accompanied by DNA-condensation and ultimately the formation of DNA containing apoptotic bodies. However, no internucleosomal DNA degradation or endogenous endonuclease activity could be detected in the cells of the monolayer or in the mainly dead and detached cells of the culture supernatant. DNA fragmentation was only observed when isolated MCF-7 nuclei were incubated with exogenous endonucleases. However, as determined by reverse transcriptase/polymerase chain reaction ***amplification*** , MCF-7 cells do express the mRNA for DNase I, an endonuclease known to be involved in apoptosis. Thus, apoptosis is part of the growth-inhibitory process and occurs without apparent internucleosomal DNA fragmentation in MCF-7 cell cultures.

L22 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:729751 CAPLUS
DOCUMENT NUMBER: 123:220263
TITLE: Repeat sequence chromosome-specific nucleic acid probes and methods for their preparation and use
INVENTOR(S): Weier, Heinz Ulrich G.; Gray, Joe W.
PATENT ASSIGNEE(S): Reagents of the University of California, USA
SOURCE: U.S., 32 pp. Cont.-in-part of U.S. Ser. No. 683,441, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5427932	A	19950627	US 1992-858124	19920326
CA 2065697	AA	19921010	CA 1992-2065697	19920408
EP 511750	A1	19921104	EP 1992-303159	19920409
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, PT, SE				
JP 06086697	A2	19940329	JP 1992-117042	19920409
PRIORITY APPLN. INFO.:			US 1991-683441	19910409
			US 1992-858124	19920326

printed

AB A primer-directed DNA ***amplification*** method is provided to efficiently isolate chromosome-specific repeated DNA using degenerate oligonucleotide primers. The probes produced are a heterogeneous mixt. that can be used with blocking DNA as a chromosome-specific staining reagent, and/or the elements of the mixt. can be ***screened*** for high specificity, size, and/or high degree of repetition among other parameters. The degenerate primers are sets of primers that vary in sequence but are substantially complementary to highly repeated nucleic acid sequences, preferably clustered within the template DNA, for example, pericentromeric alpha satellite repeat sequences. The template DNA is preferably chromosome-specific. Exemplary primers and probes are disclosed. The probes can be used to det. the no. of chromosomes of a specific type in metaphase spreads, in germ line, and/or somatic cell interphase nuclei, ***micronuclei*** , and/or in tissue sections. Also provided is a method to select arbitrarily repeat sequence probes that can be ***screened*** for chromosome specificity.

L22 ANSWER 13 OF 20 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 94180790 MEDLINE
DOCUMENT NUMBER: 94180790
TITLE: Analysis of ***micronuclei*** induced in mouse early spermatids by mitomycin C, vinblastine sulfate or etoposide using fluorescence in situ hybridization.
AUTHOR: Kallio M; Lahdetie J
CORPORATE SOURCE: Department of Medical Genetics, University of Turku, Finland.
SOURCE: MUTAGENESIS, (1993 Nov) 8 (6) 561-7.
Journal code: MUG. ISSN: 0267-8357.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406

AB Non-radioactive in situ hybridization with mouse centromere specific (major) gamma satellite DNA probe was used to analyze the mechanism of induction of spermatid ***micronuclei*** (MN) caused by the alkylating agent mitomycin C (MMC), the spindle poison vinblastine sulfate (VBL) or the DNA topoisomerase II inhibitor etoposide (VP-16). Male mice were ***treated*** with a single i.p. injection of 25 mg/kg VP-16, 5 mg/kg MMC or 2 mg/kg VBL, respectively. After 24 h (VP-16, VBL) or 13 days (MMC) stage I spermatid slides were prepared and in situ hybridization was performed using a polymerase chain reaction ***amplified*** mouse (major) gamma satellite DNA probe. The observed MN frequencies for VP-16 and MMC, 6.2/1000 and 7.5/1000 round spermatids, respectively, show a strong mutagenic effect on mouse germ cells compared with controls (1.4/1000 spermatids). VBL, on the contrary, induced a much lower total frequency of MN (2.8/1000 spermatids) compared with previous results on mouse somatic cells. Of MN in controls, 24% carried a FISH signal. After correcting for background, MMC induced 38.6% signal-positive MN, consistent with a predominantly clastogenic mode of action, while VBL induced 67.9% signal-positive MN, consistent with a mainly aneugenic mechanism. VP-16 induced 65.5% signal-positive MN, indicating that its MN-inducing capacity is mainly due to whole chromosome lagging.

L22 ANSWER 14 OF 20 MEDLINE
ACCESSION NUMBER: 94017836 MEDLINE
DOCUMENT NUMBER: 94017836
TITLE: ***Micronuclei*** : a potential intermediate marker for chemoprevention of aerodigestive tract cancer.
AUTHOR: Benner S E; Wargovich M J; Lippman S M; Hong W K
CORPORATE SOURCE: Department of Thoracic/Head and Neck Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030..
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY. SUPPLEMENT, (1993) 17F 250-4. Ref: 20
Journal code: K8K. ISSN: 0733-1959.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
AB Because they may be used as a quantifiable estimate of the extent of recent DNA injury, ***micronuclei*** , ***extrachromosomal*** fragments of DNA, are among the most studied potential intermediate markers of cancer chemoprevention. Serial measurements of ***micronuclei*** frequency may be easily performed on scrapings from the oral cavity or on bronchial brushings. Assessment of ***micronuclei*** frequency and its response to chemopreventive agents has been incorporated into studies of upper aerodigestive tract and lung cancer chemoprevention. These studies have helped define the characteristics of ***micronuclei*** and have suggested a role for this test in future chemoprevention studies. ***Micronuclei*** frequency has been shown to be increased in the oral and bronchial mucosa of individuals with known carcinogen exposure and is higher at the site of the greatest carcinogen exposure, such as the site where tobacco quids are held, than in grossly normal-appearing mucosa. ***Treatment*** with chemopreventive agents leads to a reduction in ***micronuclei*** frequency. In oral leukoplakia studies, this effect followed ***treatment*** with beta-carotene, retinol, alpha-tocopherol, and 13-cis-retinoic acid. The multistep process of epithelial carcinogenesis results from DNA damage and specific genetic events. That ***micronuclei*** reflect ongoing DNA injury suggests the hypothesis that long term suppression of cellular genotoxicity, as reflected by a reduction in ***micronuclei*** frequency, ultimately leads to a reduction in cancer incidence.

L22 ANSWER 15 OF 20 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93252964 EMBASE
DOCUMENT NUMBER: 1993252964
TITLE: ***Micronuclei*** : A potential intermediate marker for chemoprevention of aerodigestive tract cancer.
AUTHOR: Benner S.E.; Wargovich M.J.; Lippman S.M.; Hong W.K.
CORPORATE SOURCE: Department of Thoracic/Head, and Neck Medical Oncology, UT M.D. Anderson Cancer Ctr, Box 80, 1515 Holcombe Boulevard,Houston, TX 77030-4095, United States
SOURCE: Journal of Cellular Biochemistry, (1993) 52/SUPPL. 17 F (250-254).
ISSN: 0730-2312 CODEN: JCEBD5
COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 011 Otorhinolaryngology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Because they may be used as a quantifiable estimate of the extent of recent DNA injury, ***micronuclei*** , ***extrachromosomal*** fragments of DNA, are among the most studied potential intermediate markers of cancer chemoprevention. Serial measurements of ***micronuclei*** frequency may be easily performed on scrapings from the oral cavity or on bronchial brushings. Assessment of ***micronuclei*** frequency and its response to chemopreventive agents has been incorporated into studies of upper aerodigestive tract and lung cancer chemoprevention. These studies have helped define the characteristics of ***micronuclei*** and have suggested a role for this test in future chemoprevention studies. ***Micronuclei*** frequency has been shown to be increased in the oral and bronchial mucosa of individuals with known carcinogen exposure and is higher at the site of the greatest carcinogen exposure, such as the site where tobacco quids are held, than in grossly normal-appearing mucosa. ***Treatment*** with chemopreventive agents leads to a reduction in ***micronuclei*** frequency. In oral leukoplakia studies, this effect followed ***treatment*** with .beta.-carotene, retinol, .alpha.-tocopherol, and 13-cis-retinoic acid. The multistep process of epithelial carcinogenesis results from DNA damage and specific genetic events. That ***micronuclei*** reflect ongoing DNA injury suggests the hypothesis that long term suppression of cellular genotoxicity, as reflected by a reduction in ***micronuclei*** frequency, ultimately leads to a reduction in cancer incidence.

L22 ANSWER 16 OF 20 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 92390408 MEDLINE
DOCUMENT NUMBER: 92390408
TITLE: Elimination of ***extrachromosomally*** ***amplified*** MYC genes from human tumor cells reduces their tumorigenicity.
AUTHOR: Von Hoff D D; McGill J R; Forseth B J; Davidson K K; Bradley T P; Van Devanter D R; Wahl G M
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center, San Antonio 78284.
CONTRACT NUMBER: U01 CA 48405 (NCI)
R01GM27754 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Sep 1) 89 (17) 8165-9.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199212
AB Oncogene ***amplification*** has been observed in a broad spectrum of human tumors and has been associated with a poor prognosis for patients with several different types of malignancies. Importantly, at biopsy, the ***amplified*** genes localize to acentric ***extrachromosomal***

elements such as double-minute chromosomes (DMs) in the vast majority of cases. We show here that ***treatment*** of several human tumor cell lines with low concentrations of hydroxyurea accelerates the loss of their ***extrachromosomally*** ***amplified*** oncogenes. The decreases in MYC copy number in a human tumor cell line correlated with a dramatic reduction in cloning efficiency in soft agar and tumorigenicity in nude mice. No effect on gene copy number or tumorigenicity was observed for a closely related cell line containing the same number of chromosomally ***amplified*** MYC genes. One step involved in the accelerated loss of ***extrachromosomal*** elements is shown to involve their preferential entrapment of DMs within ***micronuclei*** . The data suggest that agents that accelerate the loss of ***extrachromosomally*** ***amplified*** genes could provide valuable tools for moderating the growth of a large number of human neoplasms.

L22 ANSWER 17 OF 20 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 92251702 MEDLINE
DOCUMENT NUMBER: 92251702
TITLE: A method for the ***amplification*** of Paramecium micronuclear DNA by polymerase chain reaction and its application to the central repeats of Paramecium primaurelia G surface antigen genes.
AUTHOR: Caron F; Ruiz F
CORPORATE SOURCE: Laboratoire de Genetique Moleculaire, Ecole Normale Superieure, Paris, France..
SOURCE: JOURNAL OF PROTOZOOLOGY, (1992 Mar-Apr) 39 (2) 312-8. Journal code: JT3. ISSN: 0022-3921.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
AB This paper describes a method which allows the ***amplification*** of Paramecium micronuclear DNA. Amacronucleate cells are first obtained by an appropriate ***treatment*** with nocodazole, a microtubule depolymerizing agent which blocks the elongation of the macronucleus and the distribution of the ***micronuclei*** at cell division between the two daughter cells; then, DNA from such cells is ***amplified*** by the polymerase chain reaction technique. We have applied this method to the problem of the central repeats of the G surface antigen of P. primaurelia (strain 156). The central repeats consist of a 74 amino acid sequence repeated in tandem. The sequence identity of these repeats is also found in the nucleotide sequence even at silent codon positions, suggesting the existence of a mechanism of identity maintenance acting at the nucleotide level. Mechanisms based on RNA secondary structure which are frequently proposed as an explanation of this phenomenon are unlikely to be valid in this case. One can, therefore, imagine that these repeats might originate from one micronuclear sequence through duplicative processes which could occur during the formation of the macronucleus. We have used the described technique to amplify the micronuclear version of the central repeats and showed that it is identical to the macronuclear version, thus ruling out the above hypothesis. Therefore, intragenic recombination appears to be the most likely explanation of the sequence identity of these central repeats.

L22 ANSWER 18 OF 20 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 91035544 MEDLINE
DOCUMENT NUMBER: 91035544
TITLE: Mutagenic and genotoxic activities of extracts derived from
the cooked and raw edible mushroom Agaricus bisporus.
AUTHOR: Pool-Zobel B L; Schmezer P; Sinrachatanant Y; Kliagasioglu F; Reinhart K; Martin R; Klein P; Tricker A R
CORPORATE SOURCE: Institute for Toxicology and Chemotherapy, German Cancer Research Center, Heidelberg..
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1990) 116 (5) 475-9.
Journal code: HL5. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199102

AB A. bisporus has been reported to be carcinogenic to mice [Toth et al. (1986) Cancer Res 38:177-180] and mutagenic in Salmonella typhimurium [Sterner et al. (1982) Mutat Res 101:269-281]. The effects of different heat ***treatments*** on the mutagenicity of raw, cooked (boiled) and fried A. bisporus extracts in the S. typhimurium test is reported. The spectrum of potential mutagenic activity of A. bisporus extracts was tested in vitro in Syrian hamster embryo cells for selective DNA ***amplification*** and in primary rat hepatocytes for DNA single-strand
breaks. DNA single-strand breaks were also determined in liver cells of rats and ***micronuclei*** were measured in bone marrow cells of mice in vivo following oral application of A. bisporus extracts. It was shown that the complex A. bisporus extracts per se are not detectably mutagenic in S. typhimurium and that the previously observed increase in number of colonies per plate is probably due to a histidine artefact. No indication of genotoxicity was seen in the two in vitro assays with primary mammalian
cells with two different end points. No evidence of in vivo genotoxic effects was observed in the rat liver cells. Finally, A. bisporus was not genotoxic in the micronucleus assay of mouse bone marrow cells in contrast
to its previously reported carcinogenicity in mice.

L22 ANSWER 19 OF 20 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 90058519 MEDLINE
DOCUMENT NUMBER: 90058519
TITLE: Model for the formation of double minutes from prematurely condensed chromosomes of replicating ***micronuclei*** in drug- ***treated*** Chinese hamster ovary cells undergoing DNA ***amplification*** .
AUTHOR: Sen S; Hittelman W N; Teeter L D; Kuo M T
CORPORATE SOURCE: Division of Laboratory Medicine, University of Texas M.D. Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: GM28573 (NIGMS)
GA43621 (NCI)
CA27931
+
SOURCE: CANCER RESEARCH, (1989 Dec 1) 49 (23) 6731-7.
Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199003
AB Double minutes (DM) have been associated with ***gene*** ***amplification*** in drug-resistant cells and tumor cells. However, the mechanisms by which DM are formed have not been elucidated. We present here a model to describe a possible mechanism of DM formation based on the observations made in two independent early drug-selected multidrug-resistant cell lines and from in vitro somatic cell fusion experiments between synchronized S- and M-phase cells. The multidrug-resistant cell lines contain both DM and ***amplified*** mdr (P-glycoprotein) gene. Cytogenetic analyses of cells at early stages of selection revealed the presence of a number of ***micronuclei*** in a subpopulation of these cells. These ***micronuclei*** were often asynchronous in their progression through the cell cycle. As a result, premature condensation of micronuclear chromatin was often observed in metaphase plates. The pulverized chromatin pattern seen in certain instances of S-phase prematurely condensed chromosomes displays a striking resemblance to DM structures. These DM-like structures are linked by replicating DNA as revealed by DNA labeling experiments. Somatic cell hybrids between S- and M-phase cells when grown in vitro demonstrated that S-phase prematurely condensed chromatin indeed gives rise to extra chromosomal structures in the successive cell generations. It is hypothesized that distinct DM-like structures may arise from the partially replicated and prematurely condensed S-phase chromosomes following their liberation as extra chromosomal entities after replication and/or recombination in the succeeding division cycle(s). The enrichment for DM containing specific genes in drug-resistant cells may result from the subsequent drug selections.

L22 ANSWER 20 OF 20 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 87129413 MEDLINE
DOCUMENT NUMBER: 87129413
TITLE: Cytogenetic studies on human breast carcinomas.
AUTHOR: Gebhart E; Bruderlein S; Augustus M; Siebert E; Feldner J; Schmidt W
SOURCE: BREAST CANCER RESEARCH AND TREATMENT, (1986) 8 (2) 125-38. Journal code: A8X. ISSN: 0167-6806.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198706
AB Cytogenetic studies were performed on cell material obtained from surgical specimens of 50 human breast carcinomas and from 61 cancerous effusions of 46 patients. Classical cytogenetic analyses of numerical chromosome changes and marker chromosomes revealed the non-random involvement of chromosomes #X and #22 as monosomics, of chromosomes #3, #7, and #19 as trisomics, and chromosome #1 (particularly p 13 to q 12) in marker formation. Karyotypic evolution was followed in vitro and in vivo and showed a highly individualistic pattern of stability and variability. In

addition, a systematic ***screening*** for the presence of cytogenetic equivalents of ***gene*** ***amplification*** (double minutes 'DM', homogeneously staining regions 'HSR') was carried out. A high incidence of DM-positive cases was detected in primary tumors (48%) as well as in metastatic cells from effusions (40%), with the frequency of DM-containing metaphases ranging from 1 to 100% in the positive cases. This finding supports the assumption of the fundamental biological importance of ***gene*** ***amplification*** in human solid tumors. Furthermore, chromosome breakage and ***micronuclei*** were observed in breast carcinoma cells as an apparent consequence of therapy-independent mutability.

L17 ANSWER 1 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:157655 CAPLUS
DOCUMENT NUMBER: 132:204007
TITLE: Method for isolation of extrachromosomal amplified genes by using low concentrations of ***hydroxyurea***
INVENTOR(S): Wahl, Geoffrey M.; Shimizu, Noriaki
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: U.S., 15 pp., Cont. of U.S. Ser. No. 452,275, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6033849	A	20000307	US 1996-704391	19960826
PRIORITY APPLN. INFO.:			US 1995-452275	19950526

AB The present invention provides a method for the isolation of extrachromosomal amplified nucleic acids that are assocd. with a cell proliferative disorder. Isolation and further identification of such genes is crit. for diagnosis, prognosis, and course of therapy.
REFERENCE COUNT: 12
REFERENCE(S):
(1) Curt; J Med 1983, V308(4), P199 CAPLUS
(2) Dhar; Somatic Cell Mol Genet 1984, V10(6), P547 CAPLUS
(3) Eckhardt; Proc Natl Acad Sci USA 1994, V91, P6674 CAPLUS
(4) Hayashi; Mutation Research 1994, V307, P245 CAPLUS
(6) Sen; Genomics 1994, V19, P542 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 59 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000119366 MEDLINE
DOCUMENT NUMBER: 20119366
TITLE: Induced detachment of acentric chromatin from mitotic chromosomes leads to their cytoplasmic localization at G(1) and the micronucleation by lamin reorganization at S phase.
AUTHOR: Tanaka T; Shimizu N
CORPORATE SOURCE: Faculty of Integrated Arts, Hiroshima University,

Higashi-hiroshima, Japan.
SOURCE: JOURNAL OF CELL SCIENCE, (2000 Feb) 113 (Pt 4) 697-707.
Journal code: HNK. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY WEEK: 20000603
AB Acentric and atelomeric double minute chromatin found in human cancer cells are eliminated from cells by selective incorporation into the ***micronuclei*** . We showed previously that most of the ***micronuclei*** were formed at S phase and mediated by the nuclear bud-shaped structures that selectively entrap double minutes. In this paper, we have examined the behavior of double minutes in relation to the nuclear lamin protein in cell cycle-synchronized human COLO 320DM tumor cells. At the G(1) phase, we observed that a portion of double minutes was localized at the cytoplasm and showed no association with lamin. The frequency of this localization was increased by ***hydroxyurea*** , an inducer of ***micronuclei*** , if treated at the preceding S phase. The acentric double minutes were normally segregated to daughter cells by attaching to the mitotic chromosomes, and the ***hydroxyurea*** -treatment induced their detachment, possibly through the introduction of the double strand break. When the cells entered S phase, our data suggested that the lamin protein accumulated around the cytoplasmic double minutes at the proximity of the nucleus leading to the formation of the nuclear bud-shaped structure and the initiation of DNA replication. This association of cytoplasmic double minutes with lamin coincided with the large-scale rearrangement of the intranuclear lamin protein. The implication of these findings as well as their application to a broad spectrum of other acentric, atelomeric and autonomously replicating molecules are discussed.

L17 ANSWER 3 OF 59 MEDLINE
ACCESSION NUMBER: 2000217123 MEDLINE
DOCUMENT NUMBER: 20217123
TITLE: Selective elimination of acentric double minutes from cancer cells through the extrusion of ***micronuclei*** .
AUTHOR: Shimizu N; Shimura T; Tanaka T
CORPORATE SOURCE: Faculty of Integrated Arts and Sciences, Hiroshima University, 1-7-1 Kagamiyama, Higashi-hiroshima, Hiroshima, Japan.. shimizu@ipc.hiroshima-u.ac.jp
SOURCE: MUTATION RESEARCH, (2000 Mar 14) 448 (1) 81-90.
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200007
ENTRY WEEK: 20000701
AB Several lines of evidences from us or other authors had shown that tumor cells revert their phenotypes and differentiate by the elimination of oncogenes amplified on the acentric double minutes (DMs). The selective incorporation of DMs into the cytoplasmic ***micronuclei*** was thought to be involved in this elimination, however, the mechanism by

which the content of ***micronuclei*** was eliminated from the cells remains to be discovered. In this report, we show the finding and the characterization of the extruded ***micronuclei*** in the culture fluid of human COLO 320DM tumor line, and suggest that the extrusion of ***micronuclei*** mediates the selective elimination of DMs. The extracellular ***micronuclei*** enriched with DMs had an apparently normal cytoplasmic membrane, decondensed chromatin and nuclear lamin protein, and their DNA did not suffer any extensive degradation. These characteristics were closely related to their cytoplasmic counterpart and clearly differentiated from the apoptotic bodies. We also developed a method for purifying the extracellular ***micronuclei*** . In this paper, the implications of the micronuclear extrusion are discussed.

L17 ANSWER 4 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 2000076567 EMBASE
TITLE: Use of catalytic topoisomerase II inhibitors to probe mechanisms of chemical-induced clastogenicity in chinese hamster V79 cells.
AUTHOR: Snyder R.D.
CORPORATE SOURCE: R.D. Snyder, Dupont Pharmaceuticals, Stine Haskell Research
Center, P.O. Box 30 H1/1710, Newark, DE 19714-0030, United States. Ronald.D.Snyder@Dupontpharma.com
SOURCE: Environmental and Molecular Mutagenesis, (2000) 35/1 (13-21).
Refs: 30
ISSN: 0893-6692 CODEN: EMMUEG
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Determination of the clastogenic potential of new chemical entities, particularly pharmaceuticals, is an important part of the overall safety assessment of such drugs. It is appreciated that clastogenicity can arise from perturbation of many different cellular processes distinct from direct DNA/drug interactions. One such alternative clastogenic process is inhibition of DNA topoisomerase II, during which process the topoisomerase/DNA/drug ternary complex forms stable DNA double-strand breaks (cleavable complex), which become templates for recombinational, mutagenic, and chromosomal fragmentation events. Without extensive experimentation, it is generally not possible to distinguish clastogenicity arising from direct drug/DNA interaction from that arising from inhibition of topoisomerase II. In the present investigation, we demonstrate that specific catalytic inhibitors of DNA topoisomerase II reduce the clastogenicity of topoisomerase poisons but not that arising via nontopoisomerase-dependent mechanisms. In particular, it is shown that catalytic topoisomerase II inhibitors such as chloroquine, sodium azide, and A-74932, as well as certain intercalating agents such as 9-aminoacridine and ethidium bromide, strongly antagonize the formation of ***micronuclei*** induced by the DNA gyrase inhibitor clinafloxacin and the antitumor topoisomerase II poison etoposide. These catalytic inhibitors are also shown to antagonize the clastogenicity of experimental compounds and novel pharmaceuticals presumed to be DNA intercalating agents by virtue of their response in a cell-based bleomycin amplification

assay. We extend our previous hypothesis, suggesting that the clastogenicity of some nonstructurally alerting drugs may be due to an as yet unappreciated propensity for DNA intercalation. It is further proposed that intercalation- dependent inhibition of DNA topoisomerase II may be responsible for this clastogenicity and that this may be detected in intact mammalian cells with the use of catalytic topoisomerase inhibitors.

L17 ANSWER 5 OF 59 CAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:454270 CAPLUS
DOCUMENT NUMBER: 131:82943
TITLE: Compositions and methods for identifying therapeutic agents and for treating cells having double minute DNA
INVENTOR(S): Wahl, Geoffrey M.; Shepard, H. Michael; Shimizu, Noriaki
PATENT ASSIGNEE(S): Newbiotics, Inc., USA; The Salk Institute; Kanda, Teru
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9935292	A1	19990715	WO 1999-US601	19990111
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9922217	A1	19990726	AU 1999-22217	19990111
PRIORITY APPLN. INFO.:			US 1998-71146	19980112
			US 1998-77644	19980311
			WO 1999-US601	19990111

OTHER SOURCE(S): MARPAT 131:82943

AB Methods are provided for screening test substances for their ability to inhibit, enhance, or eliminate double minute (DM) or extrachromosomal DNA by micronucleation in cells. Also provided is a method for inducing maturation or death of a cell having the capacity to generate ***micronuclei*** . The invention also provides a method of treating a disease in a subject, the cells correlated with the disease having DM and extrachromosomal DNA as well as the capacity to generate ***micronuclei*** to capture them. Further provided is a method of detecting chromosomal and extrachromosomal DNA in a cell.

REFERENCE COUNT: 5
REFERENCE(S):
(1) Eckhardt; Proc Natl Acad Sci USA 1994, V91, P6674 CAPLUS
(2) Kanda; Current Biology 1998, V8, P377 CAPLUS
(3) Shimizu; Nature Genetics 1996, V12, P65 CAPLUS
(4) Sullivan; Methods in Cell Biology 1999, V58, P203

(5) Von Hoff; Cancer Research 1991, V51, P6273 CAPLUS

L17 ANSWER 6 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999406217 EMBASE
TITLE: Chromosomal aberrations in PARP(-/-) mice: Genome stabilization in immortalized cells by reintroduction of poly(ADP-ribose) polymerase cDNA.
AUTHOR: Simbulan-Rosenthal C.M.; Haddad B.R.; Rosenthal D.S.; Weaver Z.; Coleman A.; Luo R.; Young H.M.; Wang Z.-Q.; Ried T.; Smulson M.E.
CORPORATE SOURCE: M.E. Smulson, Dept. of Biochemistry/Molec. Biol., Georgetown Univ. School of Medicine, 3900 Reservoir Road NW, Washington, DC 20007, United States. smulson@bc.georgetown.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (9 Nov 1999) 96/23 (13191-13196).
Refs: 55
ISSN: 0027-8424 CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Depletion of poly(ADP-ribose) polymerase (PARP) increases the frequency of recombination, gene amplification, sister chromatid exchanges, and ***micronuclei*** formation in cells exposed to genotoxic agents, implicating PARP in the maintenance of genomic stability. Flow cytometric analysis now has revealed an unstable tetraploid population in immortalized fibroblasts derived from PARP(-/-) mice. Comparative genomic hybridization detected partial chromosomal gains in 4C5-ter, 5F-ter, and 14A1-C1 in PARP(-/-)mice and immortalized PARP(-/-)fibroblasts. Neither the chromosomal gains nor the tetraploid population were apparent in PARP(-/-) cells stably transfected with PARP cDNA [PARP(-/-)(+PARP)], indicating negative selection of cells with these genetic aberrations after reintroduction of PARP cDNA. Although the tumor suppressor p53 was not detectable in PARP(-/-) cells, p53 expression was partially restored in PARP(-/-) (+PARP) cells. Loss of 14D3- ter that encompasses the tumor suppressor gene Rb-1 in PARP(-/-) mice was associated with a reduction in retinoblastoma(Rb) expression; increased expression of the oncogene Jun was correlated with a gain in 4C5-ter that harbors this oncogene. These results further implicate PARP in the maintenance of genomic stability and suggest that altered expression of p53, Rb, and Jun, as well as undoubtedly many other proteins may be a result of genomic instability associated with PARP deficiency.

L17 ANSWER 7 OF 59 MEDLINE
ACCESSION NUMBER: 1999216277 MEDLINE
DOCUMENT NUMBER: 99216277
TITLE: Genotoxicity of human milk extracts and detection of DNA damage in exfoliated cells recovered from breast milk [corrected and republished in Biochem Biophys Res Commun 1999 Jun 7;259(2):319-26].
AUTHOR: Martin F L; Cole K J; Weaver G; Grover P L; Phillips D H
CORPORATE SOURCE: Institute of Cancer Research, Haddow Laboratories, Cotswold

Road, Sutton, Surrey, SM2 5NG, United Kingdom.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Apr 13) 257 (2) 319-26.
Journal code: 9Y8. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Cancer Journals; Priority Journals
ENTRY MONTH: 199907

AB Genotoxic agents of environmental or dietary origin may play a role in breast cancer initiation. The ability of extracts of human milk to cause mutations in S. typhimurium TA1538 and YG1019 and to induce ***micronuclei*** and DNA strand breaks in MCL-5 cells was investigated.

Twenty samples from different donors were analysed and of these, 6 were adjudged to produce a positive mutagenic response in one or both bacterial strains. The same samples also induced significant micronucleus formation in MCL-5 cells. In the comet assay, 13/20 samples caused DNA strand breaks in MCL-5 cells. Viable exfoliated breast cells were recovered from fresh milk samples and the ability of milk extracts to cause DNA damage in these cells was demonstrated. The results show that human milk can contain components capable of causing genotoxic damage in test systems and in human breast cells, events that may be significant in the initiation of breast cancer. Copyright 1999 Academic Press.

L17 ANSWER 8 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:187844 BIOSIS
DOCUMENT NUMBER: PREV199900187844
TITLE: ***Hydroxyurea*** ***induction*** of ***micronuclei*** in prostate cell lines.
AUTHOR(S): Rivera, O. J.; McGill, J. R.
CORPORATE SOURCE: Univ. Texas Health Sci. Cent. San Antonio, San Antonio, TX USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (March, 1999) Vol. 40, pp. 237.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania,
USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L17 ANSWER 9 OF 59 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999234288 MEDLINE
DOCUMENT NUMBER: 99234288
TITLE: Co-localization of mitochondrial and double minute DNA in the nuclei of HL-60 cells but not normal cells.
AUTHOR: Hirano T; Shiraishi K; Adachi K; Miura S; Watanabe H; Utiyama H
CORPORATE SOURCE: Life Science Group, Faculty of Integrated Arts and Sciences, Hiroshima University, Kagamiyama 1-7-1, Higashihiroshima 739-8521, Japan.
SOURCE: MUTATION RESEARCH, (1999 Apr 6) 425 (2) 195-204.
Journal code: NNA. ISSN: 0027-5107.

PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990705
AB In an attempt to isolate genes located on double minute (Dmin) DNA in HL-60 cells, we prepared DNA probe from purified ***micronuclei*** . Micronucleation was induced in HL-60 cells by treatment with ***hydroxyurea*** . Screening of a cDNA library unexpectedly produced a number of clones containing mitochondrial DNA (mtDNA) sequences. Here, we show that amplified mtDNA sequences were localized in nuclei and ***micronuclei*** of HL-60 and COLO 320DM cells, but not in nuclei of WI-38 normal human fibroblasts or peripheral blood T-cells. To unequivocally demonstrate the presence of mtDNA inside of nuclei and ***micronuclei*** , we obtained tomographic fluorescence in situ hybridization (FISH) images of mtDNA by confocal microscopy of consecutive sections of paraformaldehyde (PFA)-fixed material. We also located mtDNA in nuclear buds and purified ***micronuclei*** . Dmin DNA and mtDNA were always located at similar sites. The mechanisms of nuclear retention of mtDNA and Dmin DNA and the resulting influence on tumorigenesis are discussed. Copyright 1999 Elsevier Science B.V.

L17 ANSWER 10 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1999:248090 BIOSIS
DOCUMENT NUMBER: PREV199900248090
TITLE: Co-localization of mitochondrial and double minute DNA in the nuclei of HL-60 cells but not normal cells.
AUTHOR(S): Hirano, Tetsuo; Shiraishi, Kazunori; Adachi, Koichiro; Miura, Saori; Watanabe, Hiromi; Utiyama, Hiroyasu (1)
CORPORATE SOURCE: (1) Life Science Group, Faculty of Integrated Arts and Sciences, Hiroshima University, Kagamiyama 1-7-1, Higashihiroshima, 739-8521 Japan
SOURCE: Mutation Research, (April 6, 1999) Vol. 452, No. 2, pp. 195-204.
ISSN: 0027-5107.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In an attempt to isolate genes located on double minute (Dmin) DNA in HL-60 cells, we prepared DNA probe from purified ***micronuclei*** . Micronucleation was induced in HL-60 cells by treatment with ***hydroxyurea*** . Screening of a cDNA library unexpectedly produced a number of clones containing mitochondrial DNA (mtDNA) sequences. Here, we show that amplified mtDNA sequences were localized in nuclei and ***micronuclei*** of HL-60 and COLO 320DM cells, but not in nuclei of WI-38 normal human fibroblasts or peripheral blood T-cells. To unequivocally demonstrate the presence of mtDNA inside of nuclei and ***micronuclei*** , we obtained tomographic fluorescence in situ hybridization (FISH) images of mtDNA by confocal microscopy of consecutive sections of paraformaldehyde (PFA)-fixed material. We also located mtDNA in nuclear buds and purified ***micronuclei*** . Dmin DNA and mtDNA were always located at similar sites. The mechanisms of nuclear retention of mtDNA and Dmin DNA and the resulting influence on tumorigenesis are discussed.

L17 ANSWER 11 OF 59 MEDLINE
ACCESSION NUMBER: 1999305711 MEDLINE
DOCUMENT NUMBER: 99305711
TITLE: Chelating of iron and copper alters properties of DNA in L5178Y cells, as revealed by the comet assay.
AUTHOR: Kruszewski M; Iwanenko T; Bouzyk E; Szumiel I
CORPORATE SOURCE: Department of Radiobiology and Health Protection, Institute of Nuclear Chemistry and Technology, Warsaw, Poland.. marcinkr@orange.ichtj.waw.pl
SOURCE: MUTATION RESEARCH, (1999 May 14) 434 (1) 53-60. Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990901
AB We have previously found different proportions of iron and copper in nuclei of two sublines of murine lymphoma L5178Y (LY) and proposed a model of chromatin organization with these metal ions at the DNA attachment sites. We now examine the effect of chelators, desferal (DFO, iron-specific) and neocupreine (NEO, copper-specific) on DNA of LY-R and LY-S cells, using the comet and ***micronuclei*** frequency tests. There is less copper and more iron in LY-R nuclei than in LY-S nuclei. Accordingly, the effect of NEO is more marked in LY-R than in LY-S cells and in both sublines it is expressed as enhanced tail moment (measure of DNA damage in the comet assay) and increased ***micronuclei*** frequency. On the contrary, the effect of DFO on the tail moment is less pronounced in LY-R than in LY-S cells. With increasing DFO concentrations, there is a gradual decrease in the tail moment values below the control level in LY-S cells. In LY-R cells the tail moment values initially increase, then gradually decrease, eventually falling below the control level. This points to a dramatic conformational change that masks the effect of DNA discontinuities. The presence of the latter is indicated by the increase in ***micronuclei*** frequency. These results support the postulated differential role of iron and copper ions in maintaining the higher order DNA structure in LY sublines.

L17 ANSWER 12 OF 59 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999208096 MEDLINE
DOCUMENT NUMBER: 99208096
TITLE: Modification of tirapazamine-induced cytotoxicity in combination with mild hyperthermia and/or ***nicotinamide*** : reference to effect on quiescent tumour cells.
AUTHOR: Masunaga S; Ono K; Hori H; Kinashi Y; Suzuki M; Takagaki M; Kasai S; Nagasawa H; Uto Y
CORPORATE SOURCE: Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Osaka, Japan.
SOURCE: INTERNATIONAL JOURNAL OF HYPERTHERMIA, (1999 Jan-Feb) 15 (1) 7-16. Journal code: IJY. ISSN: 0265-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY WEEK: 19990903
AB C3H/He and Balb/c mice bearing SCC VII or EMT6/KU tumours received continuous administration of 5-bromo-2'-deoxyuridine (BrdU) for 5 days to label all proliferating (P) cells. The tumours were locally heated at 40 degrees C for 60 min and/or the tumour-bearing mice received intraperitoneal injection of ***nicotinamide*** , and then tirapazamine (TPZ) was injected intraperitoneally. Sixty minutes after TPZ injection, the tumours were excised, minced and trypsinized. The tumour cell suspensions were incubated with cytochalasin-B (a cytokinesis-blocker), and the micronucleus (MN) frequency in cells without BrdU labelling (quiescent (Q) cells) was determined using immunofluorescence staining for BrdU. The MN frequency in total (P+Q) tumour cells was determined from the tumours that were not pretreated with BrdU. The cytotoxicity of TPZ was evaluated in terms of the frequency of induced ***micronuclei*** in binuclear tumour cells (= MN frequency). In both tumour systems, the MN frequencies of Q cells were greater than those of total tumour cell populations. Mild heat treatment elevated the MN frequency in total and Q cells in both tumour systems, but the effect was more marked in Q cells. In total cells, mild heat treatment increased the MN frequency in EMT6/KU tumour cells more markedly than in SCC VII tumour cells. In contrast, in both tumour systems, ***nicotinamide*** decreased the MN frequency in both cell populations, with a greater influence on the total cells. The combination of TPZ and mild heat treatment may be useful for sensitizing tumour cells in vivo, including Q cells.

L17 ANSWER 13 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 1998389546 EMBASE
TITLE: Mechanism of biochemical action of substituted 4-methylbenzopyran-2-ones. Part II: Mechanism-based inhibition of rat liver microsome-mediated aflatoxin B1-DNA binding by the candidate antimutagen 7,8-diacetoxy-4-methylcoumarin.
AUTHOR: Raj H.G.; Parmar V.S.; Jain S.C.; Goel S.; Singh A.; Gupta K.; Rohil V.; Tyagi Y.K.; Jha H.N.; Olsen C.E.; Wengel J.
CORPORATE SOURCE: V.S. Parmar, Department of Chemistry, University of Delhi, Delhi, India
SOURCE: Bioorganic and Medicinal Chemistry, (1998) 6/10 (1895-1904).
Refs: 49
ISSN: 0968-0896 CODEN: BMECEP
PUBLISHER IDENT.: S 0968-0896(98)00111-4
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB 7,8-Diacetoxy-4-methylcoumarin (DAMC), with no prerequisite for oxidative biotransformation has been reported to produce suicide inactivation of microsomal cytochrome P-450-catalysed formation of aflatoxin B1-8,9-oxide that binds to DNA. Parenteral administration of DAMC to rats caused

significant inhibition of AFB1 binding to hepatic DNA in vivo as well as AFB1-induced ***micronuclei*** formation in bone marrow cells. These results highlight the antimutagenic potential of DAMC. Copyright (C) 1998 Elsevier Science Ltd.

L17 ANSWER 14 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:183767 CAPLUS
DOCUMENT NUMBER: 128:225854
TITLE: Enhancement of chemosensitivity of quiescent cell populations in solid tumors by combined treatment with ***nicotinamide*** and low temperature hyperthermia
AUTHOR(S): Masunaga, Shin-Ichiro; Ono, Koji; Akaboshi, Mitsuhiko; Kawai, Ken-Ichi; Suzuki, Minoru; Kinashi, Yuko; Takagaki, Masao
CORPORATE SOURCE: Research Reactor Institute, Kyoto University, Osaka, 590-04, Japan
SOURCE: Kyoto Daigaku Genshiro Jikkensho Gakujutsu Koenkai Hobunshu (1998), 32, 175-180
CODEN: KDGHEI; ISSN: 0917-1746
PUBLISHER: Kyoto Daigaku Genshiro Jikkensho
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB C3H/He and Balb/c mice bearing SCC VII and EMT6/KU tumors, resp., received continuous administration of 5-bromo-2'-deoxyuridine (BrdU) for 5 days using implanted mini-osmotic pumps to label all proliferating (P) cells. ***Nicotinamide*** was administered i.p. before cisplatin injection and/or tumors were locally heated at 40.degree. for 60 min immediately after cisplatin injection. The tumors were then excised, minced and trypsinized. The tumor cell suspensions were incubated with cytochalasin-B (a cytokinesis-blocker), and the micronucleus (MN) frequency in cells without BrdU labeling (quiescent (Q) cells) was detd. using immunofluorescence staining for BrdU. The MN frequency in total (P+Q) tumor cells was detd. from tumors that were not pretreated with BrdU labeling. The sensitivity to cisplatin was evaluated in terms of the frequency of induced ***micronuclei*** in binuclear tumor cells (MN frequency). In both tumor systems, the MN frequency in Q cells was lower than that in the total cell population. ***Nicotinamide*** treatment elevated the MN frequency in total SCC VII cells. Mild heating raised the MN frequency more markedly in Q cells than total cells. The combination of ***nicotinamide*** and mild heat treatment increased the MN frequency more markedly than either treatment alone. In total SCC VII cells, ***nicotinamide*** increased 195mPt-cisplatin uptake. Mild heating elevated 195mPt-cisplatin uptake in total EMT6/KU cells. Cisplatin-sensitivity of Q cells was lower than that of total cells in both tumor systems. ***Nicotinamide*** sensitized tumor cells including a large acutely hypoxic fraction such as those of SCC VII tumors through inhibition of the fluctuations in tumor blood flow. Tumor cells including a large chronically hypoxic fraction such as Q cells were thought to be sensitized by mild heating through an increase in tumor blood flow.

L17 ANSWER 15 OF 59 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999118274 MEDLINE
DOCUMENT NUMBER: 99118274

TITLE: Nicotinic acid supplementation: effects on niacin status, cytogenetic damage, and poly(ADP-ribosylation) in lymphocytes of smokers.
AUTHOR: Hageman G J; Stierum R H; van Herwijnen M H; van der Veer M
S; Kleinjans J C
CORPORATE SOURCE: Department of Health Risk Analysis and Toxicology, Universiteit Maastricht, The Netherlands.
SOURCE: NUTRITION AND CANCER, (1998) 32 (2) 113-20.
Journal code: 094. ISSN: 0163-5581.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY WEEK: 19990503

AB As a substrate for poly(ADP-ribose) polymerase (PARP; EC, 2.4.2.30), an enzyme that is activated by DNA strand breaks and is thought to facilitate efficient DNA repair, NAD+ and its precursor nicotinic acid (niacin) are involved in the cellular defense against DNA damage by genotoxic compounds. In this study, the effect of nicotinic acid supplementation on cytogenetic damage and poly(ADP-ribosylation) was evaluated in a human population that is continuously exposed to genotoxic agents, e.g., smokers. By use of a placebo-controlled intervention design, 21 healthy smokers received supplementary nicotinic acid at 0-100 mg/day for 14 weeks. An increased niacin status, as assessed from blood ***nicotinamide*** concentrations and lymphocyte NAD+ concentrations, was observed in groups supplemented with 50 and 100 mg/day. This effect was most pronounced in subjects with lower initial NAD+ levels. An increased niacin status did not result in decreased hypoxanthine guanine phosphoribosyltransferase variant frequencies and ***micronuclei*** induction in peripheral blood lymphocytes (PBLs). Sister chromatid exchanges in PBLs, however, were increased after supplementation with nicotinic acid. This increase was positively associated with the daily dose of nicotinic acid. No effects of nicotinic acid supplementation were found for ex vivo (+/-)-7 beta, 8 alpha-dihydroxy-9 alpha, 10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene-induced poly(ADP-ribosylation), although the small number of samples that could be analyzed (n = 12) does not allow firm conclusions. Because no evidence was found for a decrease in cigarette smoke-induced cytogenetic damage in PBLs of smokers after nicotinic acid supplementation of up to 100 mg/day, it is concluded that supplemental niacin does not contribute to a reduced genetic risk in healthy smokers.

L17 ANSWER 16 OF 59 EMBASE
ACCESSION NUMBER: 1998233803 EMBASE
TITLE: Genetically engineered cells stably expressing cytochrome P450 and their application to mutagen assays.
AUTHOR: Sawada M.; Kamataki T.
CORPORATE SOURCE: M. Sawada, Division of Environmental Hygiene, Hokkaido College of Pharmacy, Katsuraoka-cho 7-1, Otaru, Hokkaido 047-02, Japan
SOURCE: Mutation Research - Reviews in Mutation Research, (1998) 411/1 (19-43).
Refs: 152
ISSN: 1383-5742 CODEN: MRRRFK

PUBLISHER IDENT.: S 1383-5742(98)00005-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 022 Human Genetics
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Genetically engineered cells transiently and stably expressing cytochrome P450 (P450), a key enzyme for biotransformation of a wide variety of compounds, have provided new tools for investigation of P450 functions such as P450-mediated metabolic activation of chemicals. This review will focus on the development of mammalian cell lines stably expressing P450s and application to toxicology testings. Stable expression systems have an advantage over transient ones in that a series of the process from metabolic activation of test compounds to the appearance of toxicological consequences occurs entirely in the same intact cells. Indeed, many cell lines stably expressing a single form of mammalian P450 have been established so far and applied to cytotoxic or genotoxic assays, the endpoints of which contained mutations at hprt and other gene loci, chromosomal aberrations, sister chromatid exchanges, ***micronuclei*** , morphological transformation, and 32P-postlabeling. Analyses of metabolites of toxic substances have also been carried out, using the intact cells or microsomal fractions prepared from the cells. The stable expression systems clearly indicate the form of P450 enzyme capable of activating a certain chemical. More recently, coexpression of P450 together with other components of microsomal electron transfer systems such as NADPH-cytochrome P450 reductase has been successfully performed to increase the metabolic capacity of the heterologously expressed P450. In addition, to reconstruct the entire metabolic activation system for certain heterocyclic amines, cell lines which simultaneously express a form of human P450 and a phase II enzyme, N-acetyltransferase, were established. These cells were highly sensitive to some carcinogenic heterocyclic amines. In genetic toxicology, such a coexpression system for two or more enzymes will provide useful materials which mimic in vivo activation systems.

L17 ANSWER 17 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97293978 EMBASE
DOCUMENT NUMBER: 1997293978
TITLE: PARP is important for genomic stability but dispensable in apoptosis.
AUTHOR: Wang Z.-Q.; Stingl L.; Morrison C.; Jantsch M.; Los M.; Schulze-Osthoff K.; Wagner E.F.
CORPORATE SOURCE: Z.-Q. Wang, Res. Inst. of Molec. Pathology (IMP), A-1030 Vienna, Austria. zqwang@iarc.fr
SOURCE: Genes and Development, (1997) 11/18 (2347-2358).
Refs: 47
ISSN: 0890-9369 CODEN: GEDEEP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Mice lacking the gene encoding poly(ADP-ribosyl) transferase (PARP or ADPRT) display no phenotypic abnormalities, although aged mice are

susceptible to epidermal hyperplasia and obesity in a mixed genetic background. Whereas embryonic fibroblasts lacking PARP exhibit normal DNA excision repair, they grow more slowly in vitro. Here we investigated the putative roles of PARP in cell proliferation, cell death, radiosensitivity, and DNA recombination, as well as chromosomal stability.

We show that the proliferation deficiency in vitro and in vivo is most likely caused by a hypersensitive response to environmental stress. Although PARP is specifically cleaved during apoptosis, cells lacking this molecule apoptosed normally in response to treatment with anti-Fas, tumor neurosis factor .alpha., .gamma.-irradiation, and dexamethasone, indicating that PARP is dispensable in apoptosis and that PARP-/- thymocytes are not hypersensitive to ionizing radiation. Furthermore, the capacity of mutant cells to carry out immunoglobulin class switching and V(D)J recombination is normal. Finally, primary PARP mutant fibroblasts and splenocytes exhibited an elevated frequency of spontaneous sister chromatid exchanges and elevated ***micronuclei*** formation after treatment with genotoxic agents, establishing an important role for PARP in the maintenance of genomic integrity.

L17 ANSWER 18 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1998097576 EMBASE

TITLE: Citrus auraptene inhibits chemically induced colonic aberrant crypt foci in male F344 rats.

AUTHOR: Tanaka T.; Kawabata K.; Kakumoto M.; Makita H.; Hara A.; Mori H.; Satoh K.; Hara A.; Murakami A.; Kuki W.; Takahashi Y.; Yonei H.; Koshimizu K.; Ohigashi H.

CORPORATE SOURCE: T. Tanaka, First Department of Pathology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

SOURCE: Carcinogenesis, (1997) 18/11 (2155-2161).
Refs: 54
ISSN: 0143-3334 CODEN: CRNGDP

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The modifying effect of dietary administration of auraptene isolated from the peel of citrus fruit (Citrus natsudaidai Hayata) on the development of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) was investigated in rats. Male F344 rats were given s.c. injections of AOM (15 mg/kg body wt) once a week for 3 weeks to induce ACF. They also received diets containing 100 or 500 p.p.m. auraptene for 5 weeks, starting 1 week before the first dose of AOM. At termination of the study (week 5) dietary administration of auraptene caused a significant reduction in the frequency of ACF in a dose-dependent manner ($P < 0.05$). Feeding of auraptene suppressed expression of cell proliferation biomarkers (5-bromo-2'-deoxyuridine labeling-index, ornithine decarboxylase activity, polyamine content and number of silver stained nucleolar organizer region protein particles) in the colonic mucosa and the occurrence of ***micronuclei*** caused by AOM. Also, auraptene increased the

activities of phase II enzymes (glutathione S-transferase and quinone reductase) in the liver and colon. These findings might suggest that inhibition of AOM-induced ACF may be associated, in part, with increased activity of phase II enzymes in the liver and colon and suppression of cell proliferation in the colonic mucosa.

L17 ANSWER 19 OF 59 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97471668 MEDLINE
DOCUMENT NUMBER: 97471668
TITLE: Augmentation in chemosensitivity of intratumor quiescent cells by combined treatment with ***nicotinamide*** and mild hyperthermia.
AUTHOR: Masunaga S; Ono K; Akaboshi M; Kawai K; Suzuki M; Kinashi Y; Takagaki M
CORPORATE SOURCE: Radiation Oncology Research Laboratory, Kyoto University, Osaka.
SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (1997 Aug) 88 (8) 770-7.
Journal code: HBA. ISSN: 0910-5050.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199801
ENTRY WEEK: 19980104

AB C3H/He and Balb/c mice bearing SCC VII and EMT6/KU tumors, respectively, received continuous administration of 5-bromo-2'-deoxyuridine (BrdU) for 5 days using implanted mini-osmotic pumps to label all proliferating (P) cells. ***Nicotinamide*** was administered intraperitoneally before cisplatin injection and/or tumors were locally heated at 40 degrees C for 60 min immediately after cisplatin injection. The tumors were then excised, minced and trypsinized. The tumor cell suspensions were incubated with cytochalasin-B (a cytokinesis-blocker), and the micronucleus (MN) frequency in cells without BrdU labeling (quiescent (Q) cells) was determined using immunofluorescence staining for BrdU. The MN frequency in total (P+Q) tumor cells was determined from tumors that had not been pretreated with BrdU labeling. The sensitivity to cisplatin was evaluated in terms of the frequency of induced ***micronuclei*** in binuclear tumor cells (MN frequency). In both tumor systems, the MN frequency in Q cells was lower than that in the total cell population.
Nicotinamide treatment elevated the MN frequency in total SCC VII cells. Mild heating raised the MN frequency more markedly in Q cells than in total cells. The combination of ***nicotinamide*** and mild heat treatment increased the MN frequency more markedly than either treatment alone. In total SCC VII cells, ***nicotinamide*** increased 195mPt-cisplatin uptake. Mild heating elevated 195mPt-cisplatin uptake in total EMT6/KU cells. Cisplatin-sensitivity of Q cells was lower than that of total cells in both tumor systems. ***Nicotinamide*** sensitized tumor cells including a large acutely hypoxic fraction, such as those of SCC VII tumors, through inhibition of the fluctuations in tumor blood flow. Tumor cells including a large chronically hypoxic fraction such as Q cells were thought to be sensitized by mild heating through an increase in tumor blood flow.

L17 ANSWER 20 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97207298 EMBASE
DOCUMENT NUMBER: 1997207298
TITLE: The role of poly(ADP-ribose) polymerase in the induction of sister chromatid exchanges and ***micronuclei*** by mitomycin C in Down's syndrome cells as compared to euploid cells.
AUTHOR: Caria H.; quintas A.; Chaveca T.; Rueff J.
CORPORATE SOURCE: J. Rueff, Department of Genetics, Faculty of Medical Sciences, New University of Lisbon, R. Junqueira 96, P-1300 Lisbon, Portugal
SOURCE: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, (1997) 377/2 (269-277).
Refs: 28
ISSN: 0027-5107 CODEN: MRFMEC
PUBLISHER IDENT.: S 0027-5107(97)00086-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Inhibitors of poly(ADP-ribose)polymerase (PARP; EC 2.4.2.30), such as 3-aminobenzamide (3-AB), can be used to assess the role of the enzyme in the induction of DNA lesions in euploid cells as compared to cells of genetic conditions known to exhibit increased susceptibility to chemical or physical mutagens, such as Down's syndrome (DS) lymphocytes. We report in this work on the effect of PARP inhibition by 3-AB in the induction of sister chromatid exchanges (SCE) and ***micronuclei*** (MN) in DS lymphocytes as compared to lymphocytes from normal controls exposed in vitro to a gradient of mitomycin C (MMC). For both types of cells, DS and normal lymphocytes, MMC induces a significant increase in frequencies of SCE and MN in the absence and in the presence of 3-AB. In the presence of 3-AB the yield of SCE and MN induced by MMC was significantly higher in normal lymphocytes as compared to lymphocytes from DS patients. The molecular mechanisms by which 3-AB affects the yield of SCE and MN remains to be fully elucidated; however, it seems clear that DS patients display a different behavior in what concerns poly(ADP-ribosyl)ation as compared to normal individuals.

L17 ANSWER 21 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:156849 CAPLUS
DOCUMENT NUMBER: 126:260325
TITLE: Structural and mechanistic bases for the induction of mitotic chromosomal loss and duplication ('malsegregation') in the yeast Saccharomyces cerevisiae: Relevance to human carcinogenesis and developmental toxicology
AUTHOR(S): Liu, Mei; Grant, Stephen G.; Macina, Orest T.; Klopman, Gilles; Rosenkranz, Herbert S.

CORPORATE SOURCE: Department of Environmental and Occupational Health, University of Pittsburgh, 260 Kappa Drive, Pittsburgh, PA, 15238, USA
SOURCE: Mutat. Res. (1997), 374(2), 209-231
CODEN: MUREAV; ISSN: 0027-5107
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MultiCASE has the ability to automatically det. the structural features responsible for the biol. activity of chems. In the present study, 93 chems. tested for their ability to induce chromosomal 'malsegregation' in the yeast Saccharomyces cerevisiae were analyzed. This 'malsegregation' mimics mol. events that occur during human development and carcinogenesis resulting in an effective loss of one chromosome of an autosomal pair and duplication of the homolog. Structural features assocd. with the ability to induce such chromosome loss and duplication were identified and compared with those obtained from examn. of other toxicol. data bases. The most significant structural similarities were identified between the induction of chromosomal malsegregation and several toxicol. phenomena such as cellular toxicity, induction of sister chromatid exchanges in vitro and rodent developmental toxicity. Very significant structural similarities were also found with systemic toxicity, ***induction*** of ***micronuclei*** in vivo and human developmental toxicity. Less significant structural overlaps were found between yeast malsegregation and rodent carcinogenicity, DNA reactivity and mutagenicity, and the induction of chromosome aberrations in vitro and sister chromatid exchanges in vivo. These overlaps may indicate mechanistic similarities between the induction of chromosomal malsegregation and other toxicol. phenomena. The predictivity of the SAR model derived from the present data base is relatively low, however. This may be merely a reflection of the small size and compn. of the data base, however, further analyses suggest that it reflects primarily the multiple mechanisms responsible for the induction of chromosomal malsegregation in yeast and the complexity of the phenomenon.

L17 ANSWER 22 OF 59 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998081605 MEDLINE
DOCUMENT NUMBER: 98081605
TITLE: Piperine inhibits aflatoxin B1-induced cytotoxicity and genotoxicity in V79 Chinese hamster cells genetically engineered to express rat cytochrome P4502B1.
AUTHOR: Reen R K; Wiebel F J; Singh J
CORPORATE SOURCE: Regional Research Laboratory, C.S.I.R., Jammu-Tawi, India.
SOURCE: JOURNAL OF ETHNOPHARMACOLOGY, (1997 Nov) 58 (3) 165-73.
Journal code: K8T. ISSN: 0378-8741.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY WEEK: 19980402

AB We have investigated the potential of piperine for inhibiting the activity of cytochrome P4502B1 and protecting against aflatoxin B1 (AFB1) in V79MZr2B1 (r2B1) cells, i.e. V79 Chinese hamster cells engineered for the expression of rat CYP4502B1. The cells were found to contain high activities of 7-methoxycoumarin demethylase (MOCD). Piperine inhibited

MOCD in preparations of r2B1 cells with an IC50 of approximately 10 microM. The cells in culture dealkylated 7-methoxycoumarin (MOC) to 7-OH-***coumarin*** linearly, at least for 12 h, where piperine produced concentration-dependent inhibition with IC50 < 30 microM. The time required for maximal inhibition was approximately 8 h with both 30 and 60 microM concentrations of piperine used. AFB1 at 0.1-20 microM caused a concentration dependent decrease in the amount of DNA and an increase in the formation of ***micronuclei*** (MN). The mycotoxin at 10 microM reduced DNA by approximately 30% and increased MN appearance by 20-fold against the background level of 7 MN per 500 nuclei. Piperine at 60 microM completely counteracted cytotoxicity and formation of MN by 10 microM AFB1 and reduced the toxic effects of 20 microM AFB1 by > 50%. The results suggest that: (i) Piperine is a potent inhibitor of rat CYP4502B1 activity; (ii) AFB1 is activated by r2B1 cells to cytotoxic and genotoxic metabolites; and (iii) piperine counteracts CYP4502B1 mediated toxicity of AFB1 in the cells and might, therefore, offer a potent chemopreventive effect against procarcinogens activated by CYP4502B1.

L17 ANSWER 23 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97233547 EMBASE
DOCUMENT NUMBER: 1997233547
TITLE: Application of the in vitro rat hepatocyte micronucleus assay in genetic toxicology testing.
AUTHOR: Muller-Tegethoff K.; Kersten B.; Kasper P.; Muller L.
CORPORATE SOURCE: K. Muller-Tegethoff, Fed.Inst. Drugs and Medical Devices, Seestr. 10, 13353 Berlin, Germany
SOURCE: Mutation Research - Genetic Toxicology and Environmental Mutagenesis, (1997) 392/1-2 (125-138).
Refs: 82
ISSN: 1383-5718 CODEN: MRGMFI
PUBLISHER IDENT.: S 0165-1218(97)00051-7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The investigation of ***micronuclei*** in mitogenic stimulated hepatocytes in vitro is a quite new area of research. Nevertheless, a relatively large database comprising more than 40 tested compounds of various classes has been generated up to now. This paper reviews the available data for the in vitro rat hepatocyte micronucleus assay, showing a sensitivity of this assay in identifying mutagens and genotoxic liver carcinogens of about 85%. Additionally, all of the tested non-carcinogens gave negative results. The use of primary hepatocytes instead of permanently dividing mammalian cell lines for the investigation of micronucleus induction has several advantages. (1) The broad spectrum of metabolizing enzymes expressed in primary hepatocytes ensures an adequate activation of most xenobiotics. (2) No transfer of activated metabolites via the culture medium is necessary in this system, since the metabolizing cells are the target cells themselves. (3) Whilst in experiments with permanently dividing cells the use of S9-mix restricts the treatment period with the test compounds to 2-6 h, in the hepatocyte micronucleus

assay continuous treatment of up to 48 h is possible. Investigations with the pyrrolizidine alkaloids retrorsine, monocrotaline and isatidine, strong mutagens and liver carcinogens, clearly showed that at least for isatidine a prolonged exposure period is essential to detect its mutagenic potential. This compound gave positive results in rat hepatocytes but not in V79-cells/S9-mix cultures. (4) The results obtained with the hepatocyte micronucleus assay are in good agreement with the genotoxic profiles of most of the compounds tested. Only three polycyclic aromatic hydrocarbons led to 'false-negative' results, since they strongly inhibited hepatocyte proliferation and thereby prevented micronucleus formation. (5) Hepatocytes are target cells of special interest when compounds are investigated which act specifically in the liver. Especially for hepatocarcinogens classified as non-genotoxins in standard genotoxicity tests or for chemicals showing DNA-repair induction in hepatocytes but no mutagenicity in standard tests, the hepatocyte micronucleus assay can contribute to clarify the situation. (6) The rat hepatocyte micronucleus assay can be performed easily and without great efforts in parallel to the in vitro hepatocyte DNA repair test (UDS-test), using the same hepatocyte batches. (7) Similar to the two versions of the UDS-test, the hepatocyte micronucleus assay can be performed following an in vivo-in vitro protocol. In order to further validate the hepatocyte micronucleus assay, as a next step controlled interlaboratory studies should be initiated.

L17 ANSWER 24 OF 59 MEDLINE

ACCESSION NUMBER: 96375197 MEDLINE
DOCUMENT NUMBER: 96375197
TITLE: An attempt to enhance chemosensitivity of quiescent cell populations in solid tumors by combined treatment with ***nicotinamide*** and carbogen.
AUTHOR: Masunaga S; Ono K; Akaboshi M; Kawai K; Akuta K; Takagaki M; Suzuki M; Kinashi Y; Abe M
CORPORATE SOURCE: Radiation Oncology Research Laboratory, Kyoto University, Osaka, Japan.
SOURCE: JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, (1996) 122 (9) 533-40.
Journal code: HL5. ISSN: 0171-5216.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199612

AB cis-Diamminedichloroplatinum(II) (cisplatin) was intraperitoneally injected into mice bearing SCC VII or EMT6/KU tumors after ten administrations of 5-bromo-2'-deoxyuridine (BrdU) to label all the proliferating tumor cells. The tumors were excised 1 h after the cisplatin injection, minced, and trypsinized. The tumor cell suspensions were then incubated with cytochalasin-B (a cytokinesis blocker). The micronucleus frequency was determined, using immunofluorescence staining for BrdU. Cells that were not labeled with BrdU were regarded as quiescent. The micronucleus frequency in the total number of tumor cells was determined in tumors that had not been pretreated with BrdU. To modify the sensitivity to cisplatin, ***nicotinamide*** was intraperitoneally injected before the administration of cisplatin or mice were placed in a circulating carbogen (95% O2, 5% CO2) chamber for 30 min after cisplatin administration. In both tumor systems, the micronucleus frequency in quiescent cells was lower than that in the total cells.

Nicotinamide pretreatment increased the micronucleus frequency in total and in quiescent cells in both tumor systems, and to a higher extent in total cells. The combination of ***nicotinamide*** and carbogen increased the micronucleus frequency more markedly than treatment with either ***nicotinamide*** or carbogen alone. In total cells of both tumors, the ***nicotinamide*** injection increased the uptake of [195mPt]cisplatin. The combined treatment raised the uptake more markedly than did treatment with either agent alone. In total cells of the SCC VII tumor, these increases in micronucleus frequency and the [195mPt]cisplatin uptake following ***nicotinamide*** or combined pretreatment were significant. In both tumors, carbogen breathing also elevated the micronucleus frequency to some degree in total and quiescent cells and the [195mPt]cisplatin uptake in total cells. The combined ***nicotinamide*** and carbogen treatment was considered to be useful for sensitizing tumor cells to chemotherapy with cisplatin in vivo.

L17 ANSWER 25 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96090119 EMBASE
DOCUMENT NUMBER: 1996090119
TITLE: Multiple pathways for apoptotic nuclear fragmentation.
AUTHOR: Dini L.; Coppola S.; Ruzittu M.T.; Ghibelli L.
CORPORATE SOURCE: Dipartimento di Biologia, Universita di Roma 'Tor Vergata', via della Ricerca Scientifica,00133 Rome, Italy
SOURCE: Experimental Cell Research, (1996) 223/2 (340-347). ISSN: 0014-4827 CODEN: ECREAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We analyzed the ultrastructure of apoptotic nuclear fragmentation in U937 cells treated with many different apoptogenic agents. We found that this characteristic apoptotic feature can be achieved through multiple alternative pathways, depending on the apoptogenic inducer, leading to slightly different final nuclear morphologies. In most instances, the irregularly shaped nucleus of U937 rounds up; then, chromatin condenses at the nuclear periphery. Condensed chromatin can form protruding patches, which eventually bud from the nucleus in sealed vesicles through a process which is actin-dependent, since it could be blocked by cytochalasins. Alternatively, chromatin condenses in tiny, nonprotruding crescents, and a cleavage in the nuclear sap forms, beginning from the inner nuclear membrane and growing inward, thus splitting the nucleus. In U937 induced to apoptosis by hydrogen peroxide in the presence of ADP-ribosylation inhibitors, the nuclei fragment in many vesicles before chromatin even begins to condense: chromatin condensation probably occurs as a consequence. While all the apoptotic morphologies described above evolve from interphase cells, a peculiar apoptotic morphology, possibly deriving from mitotic cells, is detected upon oxidative stress, recalling the formation of ***micronuclei*** by clastogenic treatments; it shows

partially membrane-bound chromatin patches, which look midway between condensed chromosomes and apoptotic condensed chromatin. The existence of these multiple pathways for nuclear fragmentation may indicate an evolutionary convergence, suggesting that this event may play an important physiological role in apoptosis.

L17 ANSWER 26 OF 59 MEDLINE
ACCESSION NUMBER: 97101621 MEDLINE
DOCUMENT NUMBER: 97101621
TITLE: Anti-BrdUrd labeling of newly synthesized DNA in HL-60 cells triggered to apoptosis.
AUTHOR: Zamai L; Falcieri E; Gobbi P; Santi S; Falconi M; Marhefka G; Vitale M
CORPORATE SOURCE: Istituto di Anatomia Umana Normale, Universit`a di Bologna, Italy.
SOURCE: CYTOMETRY, (1996 Dec 1) 25 (4) 324-32.
Journal code: D92. ISSN: 0196-4763.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY WEEK: 19970501
AB Apoptosis is an active process that takes place during pre- and postnatal life. It can be viewed as the essential counterpart to cell proliferation, both phenomena being aimed at the maintenance of tissue and organ homeostasis. Because apoptosis often takes place during the S phase of the cell cycle, we describe the spatial and temporal correlation between DNA synthesis and DNA cleavage taking place in the same nucleus at the same time as a result of the action of camptothecin on proliferating HL-60 cells in vitro. The relationship between DNA synthesis and DNA fragmentation was studied at the single-cell level by bromodeoxyuridine (BrdUrd) incorporation revealed by flow cytometry, electron microscopy, and confocal microscopy. Most HL-60 cells are triggered to apoptosis during the first hour of treatment with camptothecin, and only cells in early-middle S phase are sensitive to the drug effect, whereas late S phase cells appear insensitive to camptothecin-induced apoptosis. Our data, therefore, reinforce the hypothesis of a DNA strand break threshold that may exist in the cell, beyond which the apoptotic program is activated. Moreover, DNA synthesis activity in the nucleus committed to apoptosis is gradually downregulated; after 6 h of camptothecin treatment, virtually no residual DNA replication activity can be detected in ***micronuclei*** . DNA repair does not appear to be involved in bromode-oxyuridine incorporation during the apoptotic process.

L17 ANSWER 27 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:224850 CAPLUS
DOCUMENT NUMBER: 124:255892
TITLE: Influence of methyl derivatives of ***coumarin*** on mitotic activity and ultrastructure of meristematic cells of Allium cepa root tips
AUTHOR(S): Kupidlowska, E.; Bieniak, B.; Ruchirawat, A.; Zobel, A. M.
CORPORATE SOURCE: Anatomy and Cytology Plants, Warszaw University,

Warsaw, 00-927, Pol.
SOURCE: Phytomedicine (1996), 2(3), 275-81
CODEN: PYTOEY; ISSN: 0944-7113
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 7-Methoxy-, 7-methyl- and 6-methylcoumarins retarded mitosis in A. cepa root promeristem and caused chromosomal aberrations. Chromosomes became shorter and thicker, and often were lost during anaphase, forming ***micronuclei*** during interphase. Chromatid bridges were obsd. in anaphase and telophase, leading to the formation of a restitutional nucleus, often of irregular shape. Abnormal fragmopasts, often discontinuous, prevented normal cytokinesis. There was increased vacuolization and the mitochondria contained an electron-dense matrix. Parts of the cytoplasm, which were surrounded by ER cisternae, contained mitochondria and pieces of ER membrane. Autophagous vacuoles showed a lower d. of cytoplasm, but still contained numerous pieces of ER cisternae.

L17 ANSWER 28 OF 59 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 96387312 MEDLINE
DOCUMENT NUMBER: 96387312
TITLE: The effect of 125I decay at different stages of S-phase on survival, expression of ***micronuclei*** and chromosome aberrations in CHO cells.
AUTHOR: Ludwikow G; Hofer K G; Bao S P; Ludwikow F
CORPORATE SOURCE: Department of Radiobiology, Swedish University of Agricultural Sciences, Uppsala, Sweden.
CONTRACT NUMBER: CA 21673 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION BIOLOGY, (1996 Aug) 70 (2) 177-87.
Journal code: IRB. ISSN: 0955-3002.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199612
AB Chinese hamster ovary (CHO) cells were synchronized in M phase by mitotic selection, and then re-synchronized with ***aphidicolin*** at the G1/S phase border. The cells were labelled in early-S phase by 10 min exposure to 125I-iododeoxyuridine and then cultured (chased) in non-radioactive medium for 0.5, 3 or 5h, followed by harvesting and freezing to accumulate the desired number of 125I decays. Cell damage was assessed by evaluating colony formation, micronucleus formation and chromosome aberrations. These biological estimators of damage showed that the cytocidal effect of 125I decay increased with the duration of the post-labelling chase period: the highest level of damage was found in cells from the 5 h chase period and the lowest in the cells from the 0.5 h chase period. Survival curves for the three chase periods displayed low-dose hyper-radiosensitivity for 0 to 20 125I decays cell-1. The results indicate that the repair of DNA double-strand breaks (DSBs) may depend on the maturation stage of chromatin and an explanation of this finding is proposed which invokes the homologous recombination model for DSB repair.

L17 ANSWER 29 OF 59 MEDLINE
ACCESSION NUMBER: 97135137 MEDLINE

DOCUMENT NUMBER: 97135137
TITLE: Micronucleated erythrocytes in splenectomized patients with
and without chemotherapy.
AUTHOR: Zuniga G; Torres-Bugarin O; Ramirez-Munoz M P;
Delgado-Lamas J L; De Loza-Saldana R; Cantu J M
CORPORATE SOURCE: Division de Medicina Molecular, Centro de Investigacion
Biomedica de Occidente, I.M.S.S., Guadalajara, Jalisco,
Mexico.
SOURCE: MUTATION RESEARCH, (1996 Dec 12) 361 (2-3) 107-12.
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199703
ENTRY WEEK: 19970304
AB The purpose of the present study was to investigate the range of micronucleated erythrocytes (MNE) in peripheral blood from splenectomized patients with and without genotoxic chemotherapy. The erythrocytes were stained with Wright and Giemsa for microscopic observation. To estimate the number of MNE, two series of 10000 erythrocytes per sample were analyzed and averaged. The results expressed as mean +/- standard deviation were as follows: control patients with genotoxic chemotherapy (n = 6) 2.5 +/- 1.5 (range 1 to 5 MNE); splenectomized patients with genotoxic chemotherapy (n = 7) 65.2 +/- 17.7 (range: 47-108) MNE and splenectomized patients without genotoxic chemotherapy (n = 13) 29.5 +/- 5.8 MNE; (range: 18.5-35.6). The MNE number in the patients treated with genotoxic chemotherapy depended on the type of drugs utilized: cyclophosphamide, mitoxantrone, vincristine, busulphan, cytosine arabinoside and ***hydroxyurea*** . Upon these results, it is suggested that splenectomized people could be useful in monitoring exposures, and the baseline MNE level would serve as each person's pre-exposure control when either chronic or acute exposure to environmental mutagens is investigated.

L17 ANSWER 30 OF 59 MEDLINE
ACCESSION NUMBER: 96122041 MEDLINE
DOCUMENT NUMBER: 96122041
TITLE: Selective capture of acentric fragments by ***micronuclei*** provides a rapid method for purifying extrachromosomally amplified DNA.
AUTHOR: Shimizu N; Kanda T; Wahl G M
CORPORATE SOURCE: Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, California 92037, USA.
SOURCE: NATURE GENETICS, (1996 Jan) 12 (1) 65-71.
Journal code: BRO. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
AB The amplification and overexpression of a number of oncogenes is strongly associated with the progression of a variety of different cancers. We now present a strategy to purify amplified DNA on double minute chromosomes (DMs) to enable analysis of their prevalence and contribution to tumourigenesis. Using cell lines derived from four different tumour types,

we have developed a general and rapid method to purify ***micronuclei*** that are known to entrap extrachromosomal elements. The isolated DNA is highly enriched in DM sequences and can be used to prepare probes to localize the progenitor single copy chromosomal regions. The capture of DMs by ***micronuclei*** appears to be dependent on their lack of a centromere rather than their small size.

L17 ANSWER 31 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95349818 EMBASE
DOCUMENT NUMBER: 1995349818
TITLE: Inhibition of poly(ADP-ribose) polymerase increases (.+-.)-anti-benzo[a]pyrene diolepoxide-induced ***micronuclei*** formation and p53 accumulation in isolated human peripheral blood lymphocytes.
AUTHOR: Stierum R.H.; Van Herwijnen M.H.M.; Pasman P.C.; Hageman G.J.; Kleinjans J.C.S.; Van Agen B.
CORPORATE SOURCE: Dept Health Risk Analysis Toxicology, University of Limburg, PO Box 616,6200 MD Maastricht, Netherlands
SOURCE: Carcinogenesis, (1995) 16/11 (2765-2771).
ISSN: 0143-3334 CODEN: CRNGDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
029 Clinical Biochemistry
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In response to DNA damage, in particular DNA strand breaks, the proposed roles for normal tumour suppressor protein p53 are to increase the period of time available for DNA repair prior to replication, or to direct damaged cells into programmed cell-death. Since treatment of mammalian cells with (.+-.)-anti-benzo[a]pyrene diolepoxide [(.+-.)-anti-BPDE] - a mixture of metabolites comprising the most reactive (+)-anti-enantiomer of the full environmental carcinogen benzo[a]pyrene - has been shown to result in induction of DNA repair processes and consequently in DNA strand break formation, the aim of the present study was to investigate whether p53 accumulation is induced in (.+-.)-anti-BPDE-treated phytohaemagglutinin-stimulated human peripheral blood lymphocytes (PBLs). Both immunocytochemical and immunoblot analysis indicated that treatment of PBLs with (.+-.)-anti-BPDE results in p53 accumulation. Optimal accumulation was observed at 2.5 .mu.M, while no increase of p53 levels was observed at concentrations < 2.5 .mu.M and > 10 .mu.M. Further, (.+-.)-anti-BPDE-induced p53 accumulation in PBLs was found to be time-dependent with accumulation up to 24 h after the onset of treatment. Treatment of PBLs with 2.5 .mu.M of (.+-.)-anti-BPDE and 1 mM of 3-aminobenzamide, an inhibitor of the DNA strand break-dependent enzyme poly(ADP-ribose) polymerase, resulted in increased p53 levels, in comparison to cells treated with (.+-.)-anti-BPDE alone. This combination also potentiated the frequency of (.+-.)-anti-BPDE-induced ***micronuclei*** . These findings suggest that (.+-.)-anti-BPDE-induced DNA strand break formation is responsible for the observed p53 accumulation. It is unlikely that poly(ADP-ribose) polymer formation is a prerequisite in the process of p53 accumulation, as triggered by DNA strand-break inducing agents like (.+-.)-anti-BPDE. It is hypothesized that p53-dependent pathways may be activated in phytohaemagglutinin-

stimulated human peripheral blood lymphocytes exposed ex vivo to (.+-.)-anti-BPDE.

L17 ANSWER 32 OF 59 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 96099504 MEDLINE
DOCUMENT NUMBER: 96099504
TITLE: Evaluation studies on the in vitro rat hepatocyte micronucleus assay.
AUTHOR: Muller-Tegethoff K; Kasper P; Muller L
CORPORATE SOURCE: Federal Institute for Drugs and Medical Devices, Berlin, Germany.
SOURCE: MUTATION RESEARCH, (1995 Dec) 335 (3) 293-307. Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199603

AB Based on a previous study with 8 chemicals (Muller et al., 1993) the applicability of the in vitro rat hepatocyte micronucleus assay was evaluated by testing a further 21 compounds of different chemical classes.

The obtained results are in good agreement with the known genotoxic profiles of about 90% of the in total tested compounds. Several known mutagens and carcinogens, i.e., alkylating agents, aromatic amines, nitrosamines, nitro compounds, cross-linking agents, and pyrrolizidine alkaloids gave clear positive results in this assay, whereas all of the tested non-carcinogens were negative. The hepatocyte micronucleus assay was shown to distinguish between carcinogenic/non-carcinogenic isomers, such as 2- and 4-acetylaminofluorene (AAF) and 2- and 1-nitropropane (NP).

Furthermore, the non-genotoxic nature of several hepatocarcinogens, i.e., the peroxisome proliferating agents fenofibrate, nafenopin, Wy-14,643, diethyl(hexyl)phthalate (DEHP), and the sedative phenobarbital, could be confirmed in this assay. The hepatocarcinogen ***coumarin*** exerted mitogenic but no mutagenic properties in the rat hepatocyte micronucleus assay. This compound may act as a liver tumor promoter. Benzo[a]pyrene (B[a]P) and 7,12-dimethylbenzanthacene (DMBA), both belonging to the group of known carcinogenic and mutagenic polycyclic aromatic hydrocarbons, failed to induce micronucleus formation in rat hepatocytes. The high susceptibility of in vitro proliferating hepatocytes to mitotic inhibition, exerted by the strong cytotoxic actions of these compounds, seems to be responsible for these negative results. A strongly reduced mitotic activity can prevent the formation of ***micronuclei*** , even when clastogenic effects may have occurred. In the present stage, the in vitro rat hepatocyte micronucleus assay cannot be recommended for screening genotoxicity testing. It should rather be used for special purposes, e.g., when liver-specific mutagenic effects are expected.

L17 ANSWER 33 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V. DUPLICATE 11
ACCESSION NUMBER: 95354563 EMBASE
DOCUMENT NUMBER: 1995354563
TITLE: Antimicrotubule effects of the novel antitumor benzoylphenylurea derivative HO-221.
AUTHOR: Ando N.; Nakajima T.; Masuda H.; Kawabata Y.; Iwai M.; Watanabe M.; Kagitani Y.; Yamada N.; Tsukagoshi S.
CORPORATE SOURCE: Safety Evaluation Laboratory, The Green Cross Corporation, 214-1, Yamasaki Fukusaki-cho,Kanzaki-gun, Hyogo 679-22, Japan

SOURCE: Cancer Chemotherapy and Pharmacology, (1995) 37/1-2 (63-69).
ISSN: 0344-5704 CODEN: CCPHDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
029 Clinical Biochemistry
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The antitumor action of HO-221, a novel benzoylphenylurea derivative, was studied. The in vitro cytotoxic strength of HO-221 was investigated, as measured by IC50 values, compared with those of other drugs with different action mechanisms, using Chinese hamster lung (CHL) cells, mouse leukemia L1210 cells and human promyelocytic leukemia HL-60 cells. Morphological alterations following treatment were observed under a phase contrast microscope, and the mitotic index was determined at regular intervals to check for accumulation of metaphase cells. HO-221 was found to have a very strong toxic effect on all cell types, equal to that of the spindle poisons used as controls. HO-221 also produced the same specific morphological changes as the spindle poisons, with a significant accumulation of metaphase cells. A chromosome analysis of treated cells showed that HO-221 frequently induced polyploid and aneuploid cells, but without accompanying chromosome-breaking activity. An in vivo mouse bone marrow micronucleus assay was also carried out. The assay allowed the in vivo identification of a chromosome breaker or a spindle poison through the measurement of the relative sizes of ***micronuclei*** produced and erythrocytes. HO-221 was found frequently to induce relatively large ***micronuclei*** , an action regarded as specific to spindle poisons. It was thus demonstrated that HO-221 acts as a spindle poison both in vitro and in vivo. In order to investigate the mechanism of this action, a study of tubulin assembly using purified calf brain tubulin was carried out, which demonstrated clearly that HO-221 inhibits microtubule assembly. A detailed investigation of the action mechanism of HO-221 as a spindle poison is now called for.

L17 ANSWER 34 OF 59 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 95191595 MEDLINE
DOCUMENT NUMBER: 95191595
TITLE: The suitability of the micronucleus assay in human lymphocytes as a new biomarker of excision repair.
AUTHOR: Surralles J; Xamena N; Creus A; Marcos R
CORPORATE SOURCE: Department de Gen`etica i de Microbiologia, Universitat Aut`onoma de Barcelona, Bellaterra (Cerdanyola del Vall`es), Spain..
SOURCE: MUTATION RESEARCH, (1995 Mar) 342 (1-2) 43-59.
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199506

AB The cytokinesis blocked micronucleus assay is relatively insensitive to

detect agents that predominantly induce excision repairable DNA lesions. However, it has been recently proposed that excision-repairable DNA lesions induced in G0/G1 phase can be converted to ***micronuclei*** by using inhibitors of the gap filling step of excision repair so that unfilled gaps are converted to double stranded breaks after S phase and ***micronuclei*** (MN) at completion of mitosis. As it has been recently demonstrated this process could be improved by combining cytosine arabinoside (ARA-C) and ***hydroxyurea*** (HU). In the present work, we have investigated the suitability of this new approach by studying its ability to detect excision repairable DNA lesions induced by 10 pesticides (alachlor, atrazine, cypermethrin, deltamethrin, fenpropathrin, fenvalerate, maleic hydrazide, paraquat, permethrin and trifluralin) and 3 well-known mutagenic agents (ethyl methane sulphonate, EMS; methylnitrosourea, MNU; and mytomicin C, MMC). Our results showed that the combination of ARA-C and HU substantially increased the level of MN in whole blood lymphocyte cultures, but it provided an excess of toxicity when further treatments, such as MNU, were performed. When ARA-C alone was used, the ARA/CBMN assay appeared to be highly sensitive and specific in detecting agents known to induce excision repairable DNA lesions. Thus, EMS and MNU but not MMC greatly induced DNA excision repair. On the other hand, alachlor, permethrin and, to a lesser extent, trifluralin and fenpropathrin also increased the ratio of excision repairable DNA lesions converted to MN. On the contrary, atrazine, cypermethrin, deltamethrin, fenvalerate, maleic hydrazide and paraquat did not induce excision repair.

L17 ANSWER 35 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:802405 CAPLUS
DOCUMENT NUMBER: 123:246170
TITLE: Mechanisms of antimutagenic action of flavorings
AUTHOR(S): Ohta, Toshihiro
CORPORATE SOURCE: School of Life Science, Tokyo University of Pharmacy and Life Science, Hachioji, 192-03, Japan
SOURCE: Kankyo Hen'igen Kenkyu (1995), Volume Date 1995, 17(1), 23-33
CODEN: KHKEEN; ISSN: 0910-0865
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Some naturally occurring flavorings such as cinnamaldehyde, ***coumarin*** , anisaldehyde, and vanillin inhibited the formation of mutations in E. coli. Antimutagenic effects was obsd. on mutations induced by UV-light or 4-nitroquinoline-1-oxide, but not on those by methylating agents. These compds. did not prevent the induction of the SOS repair function. The frequency of interplasmidic recombination was significantly increased in the presence of vanillin. It is considered that these flavorings act as antimutagens by promoting the recA-dependent DNA recombinational repair system in bacteria. In mammalian cells, post-treatment with vanillin suppressed the following mutagenicity: 6-thioguanine-resistant mutations induced by UV or X-rays in cultured V79 cells, structural chromosome aberrations induced by UV, X-rays, mitomycin C, or bleomycin in CHO cells, ***micronuclei*** induced by mitomycin C in mouse bone marrow cells, and ethylnitrosourea-induced somatic mutations in the mouse spot test. Treatment with vanillin in the G2 phase of the

cell cycle suppressed breakage-type, but not exchange-type chromosome aberrations induced by UV. On the contrary, the frequency of sister chromatid exchanges (SCEs) induced by UV or mitomycin C was obviously enhanced when CHO cells were post-treated with vanillin. Since an antimutagenic compd. found in a certain condition became ineffective, or even potentiated mutations when the endpoints investigated varied, the elucidation of the mechanisms of antimutagenesis is indispensable for the evaluation of antimutagens.

L17 ANSWER 36 OF 59 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 95020691 MEDLINE
DOCUMENT NUMBER: 95020691
TITLE: The origin of ***micronuclei*** induced by cytosine arabinoside and its synergistic interaction with ***hydroxyurea*** in human lymphocytes.
AUTHOR: Fenech M; Rinaldi J; Surralles J
CORPORATE SOURCE: CSIRO, Division of Human Nutrition, Adelaide, Australia..
SOURCE: MUTAGENESIS, (1994 May) 9 (3) 273-7.
Journal code: MUG. ISSN: 0267-8357.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
AB Using human lymphocytes and the cytokinesis-block micronucleus (CBMN) assay we have recently shown that excision-repairable DNA lesions induced by methylnitrosourea (MNU) and ultraviolet (UV) light (254 nm) can be converted to ***micronuclei*** (MNi) within one cell cycle if cytosine arabinoside (ARA-C) is added during the G1 phase of the cell cycle after mitogen stimulation. We have proposed that this conversion resulted from the inhibition by ARA-C of the gap-filling step during excision repair which results in the formation of single-stranded breaks at repair sites; these breaks are then converted to chromatid or chromosome breaks and subsequently to MNi on completion of nuclear division. To confirm this hypothesis we have examined the origin of MNi induced by ARA-C by using anti-kinetochore antibodies and found that between 77 and 86% of these MNi are kinetochore-negative which supports the idea that they originate mainly from acentric chromosome fragments. We have also demonstrated that combining ARA-C treatment with ***hydroxyurea*** (HU) during G1 provides a synergistic improvement in the conversion of spontaneous (4-fold increment) or MNU-induced (2-fold increment) excision-repairable DNA lesions to MNi when compared to the effects with ARA-C alone. HU treatment on its own did not influence micronucleus expression in untreated cells and cells treated with MNU.

L17 ANSWER 37 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V. DUPLICATE 14
ACCESSION NUMBER: 94241729 EMBASE
DOCUMENT NUMBER: 1994241729
TITLE: Coumarins as antimitotics.
AUTHOR: Podbielkowska M.; Kupidlowska E.; Waleza M.; Dobrzynska K.;
Louis S.A.; Keightley A.; Zobel A.M.
CORPORATE SOURCE: Department of Chemistry, Trent University, Peterborough, Ont. K9J 788, Canada
SOURCE: International Journal of Pharmacognosy, (1994) 32/3 (262-273).
ISSN: 0925-1618 CODEN: IJPYEW
COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Coumarin*** , two of its hydroxy derivatives (umbelliferone and 4-hydroxycoumarin), and two furanocoumarins (psoralen and xanthotoxin) were investigated for their potential use as mitodepressants. In sublethal concentrations these compounds stopped mitosis (umbelliferone inhibited 95%) in 24 h incubations. All phases of mitosis were affected in the same proportions, except umbelliferone, which prolonged prophase and blocked metaphase. In postincubation, the meristematic cells kept in ***coumarin*** solution did not recover. Postincubation of umbelliferone and 4- hydroxycoumarin resulted in mitoses reaching 40% and 120% of the control, respectively. Furanocoumarins showed a few mitoses in 24 h postincubation, but after 72 h no mitoses occurred. Chromosomal aberrations were not observed after ***coumarin*** and 4-hydroxycoumarin treatment. Umbelliferone caused shortening and thickening of chromosomes, caused postponement of chromatid separation, occurrence of sticky ends leading to anaphase, and telophase bridges. Similar types of aberration, but more frequent, were observed for furanocoumarins, which additionally showed severe aberrations of fragmoplast formation leading to the occurrence of binucleate cells, ***micronuclei*** , some tetraploid nuclei with irregular surfaces, and fragmoplasts located in distant areas of the cell.

L17 ANSWER 38 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1993:433707 BIOSIS
DOCUMENT NUMBER: PREV199396088332
TITLE: The nuclear apparatus of the ditransversal ciliate Homalozoon vermiculare (Ciliophora, Rhabdophora) during interphase and division: II. The ***micronuclei*** and some observations on conjugation.
AUTHOR(S): Leipe, Detlef D. (1); Hausmann, Klauss
CORPORATE SOURCE: (1) Cent. Mol. Evol., Marine Biol. Lab., Woods Hole, Mass. 02543 USA
SOURCE: Journal of Eukaryotic Microbiology, (1993) Vol. 40, No. 4, pp. 447-458.
ISSN: 1066-5234.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The nuclear apparatus of H. vermiculare consists of a single moniliform macronucleus and about 25 ***micronuclei*** . The ***micronuclei*** are about 3 mu-m in diameter and characterized by a meshwork of thick condensed chromatin. Mitosis is intranuclear and acentric as in all other ciliates. In metaphase, interpolar and chromosomal microtubules are abundant and the length of the ***micronuclei*** increases to about 5 mu-m. In late anaphase, interzonal microtubules become prominent and the spindle elongates to about 50 mu-m. In meta- and anaphase, the microtubules of the spindle are attached to the polar vesicles, and in anaphase, chromosomes become attached to it. In contrast to most other eukaryotes, micronuclear mitosis is not strictly bound to cell division in H. vermiculare. While most of the ***micronuclei*** divide prior to cytokinesis, others retain their interphasic shape or degenerate. In addition, some ***micronuclei*** divide in the interdivision period, i.e. between two successive divisions of the cell and macronucleus. Mating

cells of H. vermiculare become joined to each other in the cilia-free region covering the cytostome. In the course of conjugation, the cell membranes and the underlying oral filamentous sheaths of both cells fuse, thus uniting the endoplasm of both cells in the mouth region. Synaptonemal complexes in the meiotic chromosomes are more distinct in H. vermiculare than in most other ciliates. The micrographs presented here depict clearly the central filament, transverse elements, and other substructures.

L17 ANSWER 39 OF 59 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 94204598 MEDLINE
DOCUMENT NUMBER: 94204598
TITLE: Chromosome aberrations in chloralkali workers previously exposed to mercury vapor.
AUTHOR: Hansteen I L; Ellingsen D G; Clausen K O; Kjuus H
CORPORATE SOURCE: Department of Occupational Medicine, Telemark Central Hospital, Skien, Norway.
SOURCE: SCANDINAVIAN JOURNAL OF WORK, ENVIRONMENT AND HEALTH, (1993 Dec) 19 (6) 375-81.
Journal code: UEB. ISSN: 0355-3140.
PUB. COUNTRY: Finland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
AB Chromosome aberrations and ***micronuclei*** in peripheral lymphocytes were studied in 29 male chloralkali workers previously exposed to mercury vapor and in two matched reference groups comprising 29 nitrate fertilizer workers and 29 customs and police officers. The study was performed using whole-blood cultures with and without ***hydroxyurea*** and caffeine to inhibit deoxyribonucleic acid synthesis and repair, respectively. No significant differences in the frequencies of chromosome aberrations and ***micronuclei*** were observed. However, a nonsignificant increase in chromosome breaks and dicentrics was found in the subgroups with high urinary mercury peak levels or high cumulative mercury exposure. An increased prevalence of "high" scores of chromatid breaks in the inhibited cultures, exceeding the 75th percentile of all of the subjects studied, was observed for the chloralkali workers when compared with both reference groups. No evident cytogenetic effects were observed among the chloralkali workers with the methods used in the present study.

L17 ANSWER 40 OF 59 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 93241195 MEDLINE
DOCUMENT NUMBER: 93241195
TITLE: Restriction-endonuclease-induced DNA double-strand breaks and chromosomal aberrations in mammalian cells.
AUTHOR: Bryant P E; Johnston P J
CORPORATE SOURCE: School of Biological and Medical sciences, University of St. Andrews, Fife, Scotland, UK.
SOURCE: MUTATION RESEARCH, (1993 May) 299 (3-4) 289-96. Ref: 31
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199307

AB Restriction endonucleases (RE) can be used to mimic and model the clastogenic effects of ionising radiation. With the development of improved techniques for cell poration: electroporation and recently streptolysin O (SLO), it has become possible more confidently to study the relationships between DNA double-strand breaks (dsb) of various types (e.g. blunt or cohesive-ended) and the frequencies of induced metaphase chromosomal aberrations or ***micronuclei*** in cytokinesis-blocked cells. Although RE-induced dsb do not mimic the chemical end-structure of radiation-induced dsb (i.e. the 'dirty' ends of radiation-induced dsb), it has become clear that cohesive-ended dsb, which are thought to be the major type of dsb induced by radiation, are much less clastogenic than blunt-ended dsb. It has also been possible, with the aid of electroporation or SLO to measure the kinetics of dsb in cells as a function of time after treatment. These experiments have shown that some RE (e.g. Pvu II) are extremely stable inside CHO cells and at high concentrations persist and induce dsb over a period of many hours following treatment. Cutting of DNA by RE is thought to be at specific recognition sequences (as in free DNA) although the frequencies of sites in native chromatin available to RE is not yet known. DNA condensation and methylation are both factors limiting the numbers of available cutting sites. Relatively little is known about the kinetics of incision or repair of RE-induced dsb in cells. Direct ligation may be a method used by cells to rejoin the bulk of RE-induced dsb, since inhibitors such as araA, araC and ***aphidicolin*** appear not prevent rejoining, although these inhibitors have been found to lead to enhanced frequencies of chromosomal aberrations. 3-Aminobenzimide, the poly-ADP ribose polymerase inhibitor is the only agent that has so far been shown to inhibit rejoining of RE-induced dsb. Data from the radiosensitive xrs5 cell line, where chromosomal aberration frequencies are higher after RE treatments than in their normal parental CHO line, indicates that the xrs dsb repair pathway is involved in the repair of these dsb. We found that cells treated simultaneous with Pvu II and T4 ligase yielded lower levels of chromosomal damage than in the WT parental line indicating that Pvu II induced dsb retain their ability to be blunt-end ligated inside the cell.

L17 ANSWER 41 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 17
ACCESSION NUMBER: 1993:365946 BIOSIS
DOCUMENT NUMBER: PREV199396051621
TITLE: Isolation of sub-diploid microprotoplasts for partial genome transfer in plants: Enhancement of micronucleation and enrichment of microprotoplasts with one or a few chromosomes.
AUTHOR(S): Ramulu, K. S. (1); Dijkhuis, P.; Famelaer, I.; Cardi, T.; Verhoeven, H. A.
CORPORATE SOURCE: (1) Dep. Cell Biol., DLO-Centre Plant Breeding Reproduction Res., PO Box 16, 6700 AA Wageningen Netherlands Antilles
SOURCE: Planta (Heidelberg), (1993) Vol. 190, No. 2, pp. 190-198.

ISSN: 0032-0935.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Results on the enhancement of the frequency of protoplasts with ***micronuclei*** , and on the isolation and enrichment of smaller sub-diploid microprotoplasts in transformed Nicotiana plumbaginifolia Viv.
are reported. Suspension cells were treated with the spindle toxin amiprophos-methyl (APM) for 48 h, and subsequently incubated in a mixture of cell-wall-digesting enzymes in the presence of APM and cytochalasin-B. During enzyme incubation, the frequency of micronucleated protoplasts increased by a factor of 2-6. A shorter period (3 h) of incubation with a higher concentration of enzymes as well as a longer period (16 h) of incubation with a lower concentration of enzymes gave similar frequencies of micronucleated protoplasts and yields of ***micronuclei*** . Further, synchronization by sequential treatment with the DNA-synthesis inhibitor hydroxy urea, or ***aphidicolin*** , followed by APM and enzyme incubation, significantly increased the frequency of micronucleated
protoplasts and the number of ***micronuclei*** . The suspension of protoplasts (mono- and micronucleated) obtained after enzyme incubation was fractionated throuh a continuous iso-osmotic gradient of Percoll, using high-speed centrifugation. This resulted in one large and a few small bands, which contained a heterogeneous population of microprotoplasts, protoplasts and cytoplasts. In contrast to the large band, the small bands contained a relatively higher frequency of small sub-diploid microprotoplasts. To separate the small sub-diploid microprotoplasts from the large microprotoplasts and protoplasts of the bands, discontinuous Percoll gradients and sequential filtration through nylon sieves of decreasing pore size (48-20-15-10-5 pm) were investigated.
Compared with the former method, the latter gave a highly enriched fraction containing predominantly (apprxeq 80%) small subdiploid microprotoplasts with DNA contents equivalent to that of one to four chromosomes, as revealed by microdensitometric and flow-cytometric analyses. The application of this technique for partial genome and limited
gene transfer is discussed.

L17 ANSWER 42 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1993:503503 BIOSIS
DOCUMENT NUMBER: PREV199396127510
TITLE: Radioprotective effects of cimetidine in mouse bone marrow cells exposed to gamma-rays as assayed by the micronucleus test.
AUTHOR(S): Mozdarani, H. (1); Gharbali, A.
CORPORATE SOURCE: (1) Sch. Med. Sci., Tarbiat Modarres Univ., P.O. Box 14155-4838, Tehran, I.R. Iran
SOURCE: International Journal of Radiation Biology, (1993) Vol. 64,
No. 2, pp. 189-194.
ISSN: 0955-3002.
DOCUMENT TYPE: Article
LANGUAGE: English
AB An in vivo micronucleus assay using mouse bone marrow for identifying the radioprotective effect of cimetidine is described. The influence of cimetidine, an antagonist to the histamine H2 receptor, on the kinetics of
radiation-induced ***micronuclei*** was tested in the CD-1 male mouse.

Cimetidine was administered at 15 mg/kg i.p. 2 h prior to irradiation of mouse given various doses of gamma-rays from 0.25 to 1 Gy. The frequency of micronucleated polychromatic erythyrocytes (PCEs) and normochromatic erythrocytes (NCEs) per 1500 PCEs were determined at 36, 48 and 72 h post-irradiation. The results obtained indicate a linear dose response for three sampling times, and that cimetidine reduces the number of ***micronuclei*** in both PCE and NCE at all sampling times, as well as reducing radiation cytotoxicity. When the overall effects of radiation alone or in the presence of cimetidine are compared, a dose reduction factor (DRF) of 1.5 was found for cimetidine in the dose range used in this study, which is statistically highly significant (p lt 0.001). This DRF at the low dosage of cimetidine used in this study compared with known radioprotectors is very promising and it might be useful as a potent radioprotector. The mechanism by which cimetidine reduces clastogenic effects of radiation is not well understood. We propose that it might act by a radical scavenging mechanism via enzyme catalysis.

L17 ANSWER 43 OF 59 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 94068962 MEDLINE
DOCUMENT NUMBER: 94068962
TITLE: Radiosensitization of SCCVII tumours and normal tissues by ***nicotinamide*** and carbogen: analysis by micronucleus assay.
AUTHOR: Ono K; Masunaga S; Akuta K; Akaboshi M; Abe M
CORPORATE SOURCE: Radiation Oncology Research Laboratory, Kyoto University Research Reactor Institute, Osaka, Japan..
SOURCE: RADIOTHERAPY AND ONCOLOGY, (1993 Aug) 28 (2) 162-7. Journal code: RAE. ISSN: 0167-8140.
PUB. COUNTRY: Ireland
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199403
AB The radiosensitizing effect on SCCVII tumours of carbogen (95% O2 + 5% CO2) combined with ***nicotinamide*** was investigated using the micronucleus assay and an in vivo/in vitro colony formation assay following single irradiation. The effects on intestinal crypt cells and bone marrow cells were also examined in mice. The frequency of ***micronuclei*** in tumours increased with an increase in the ***nicotinamide*** dose (administered 1 h before the irradiation of 5 Gy) from 0.1 to 1.0 mg/g, and showed a 1.3-fold increase at 1.0 mg/g when compared with radiation alone. The micronucleus frequency showed a more marked increase following irradiation combined with ***nicotinamide*** and carbogen inhalation starting 15 min before irradiation. The radiosensitizing effect reached a plateau at a ***nicotinamide*** dose of 0.1 mg/g in combination with carbogen, giving an enhancement ratio (ER) of 1.8 relative to radiation alone at 2 Gy. In the radiation dose range of 5-20 Gy, ERs of 1.8-1.9 and 1.5 (at a 10% cell-survival level) were obtained for the combination of 0.1 or 1.0 mg/g ***nicotinamide*** and carbogen and for carbogen alone, respectively. A slight increase in the regeneration response of the jejunum and the bone marrow was observed following irradiation combined with 0.1 mg/g ***nicotinamide*** and

carbogen, yielding ERs of 1.07 for the jejunum and 1.15 for the bone marrow. Thus, the ***nicotinamide*** /carbogen combination, with its large therapeutic gain factor at low doses and proven low toxicity in humans, seems to improve the response of cancer to radiotherapy.

L17 ANSWER 44 OF 59 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 93116772 MEDLINE
DOCUMENT NUMBER: 93116772
TITLE: Inhibition of adriamycin-induced ***micronuclei*** by desferrioxamine in Swiss albino mice.
AUTHOR: al-Shabanah O A
CORPORATE SOURCE: Department of Pharmacology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia..
SOURCE: MUTATION RESEARCH, (1993 Feb) 301 (2) 107-11.
Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199304
AB Swiss albino male mice, 6-8 weeks old, were treated i.p. with different doses of desferrioxamine dissolved in water for 7 days. Some of the mice in each group were injected i.p. with adriamycin (15 mg/kg) and killed after 30 or 24, 48 and 72 h. The femoral cells of mice in different groups were collected and studied. Desferrioxamine treatment failed to affect the incidence of ***micronuclei*** at doses of 125-250 mg/kg/day. Pretreatment with desferrioxamine was found to provide significant protection against adriamycin-induced ***micronuclei*** without interfering with its cytotoxic potential.

L17 ANSWER 45 OF 59 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 92390408 MEDLINE
DOCUMENT NUMBER: 92390408
TITLE: Elimination of extrachromosomally amplified MYC genes from human tumor cells reduces their tumorigenicity.
AUTHOR: Von Hoff D D; McGill J R; Forseth B J; Davidson K K; Bradley T P; Van Devanter D R; Wahl G M
CORPORATE SOURCE: Department of Medicine, University of Texas Health Science Center, San Antonio 78284.
CONTRACT NUMBER: U01 CA 48405 (NCI)
R01GM27754 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Sep 1) 89 (17) 8165-9.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199212
AB Oncogene amplification has been observed in a broad spectrum of human tumors and has been associated with a poor prognosis for patients with several different types of malignancies. Importantly, at biopsy, the amplified genes localize to acentric extrachromosomal elements such as double-minute chromosomes (DMs) in the vast majority of cases. We show here that treatment of several human tumor cell lines with low concentrations of ***hydroxyurea*** accelerates the loss of their extrachromosomally amplified oncogenes. The decreases in MYC copy number in a human tumor cell line correlated with a dramatic reduction in

cloning
efficiency in soft agar and tumorigenicity in nude mice. No effect on gene
copy number or tumorigenicity was observed for a closely related cell line
containing the same number of chromosomally amplified MYC genes. One step
involved in the accelerated loss of extrachromosomal elements is shown to
involve their preferential entrapment of DMs within ***micronuclei***
.
The data suggest that agents that accelerate the loss of
extrachromosomally amplified genes could provide valuable tools for
moderating the growth of a large number of human neoplasms.

L17 ANSWER 46 OF 59 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 93126093 MEDLINE
DOCUMENT NUMBER: 93126093
TITLE: Replication-dependent and independent regulation of HMG expression during the cell cycle and conjugation in Tetrahymena.
AUTHOR: Wang T; Allis C D
CORPORATE SOURCE: Department of Biology, Syracuse University, NY 13244..
CONTRACT NUMBER: GM40922 (NIGMS)
SOURCE: NUCLEIC ACIDS RESEARCH, (1992 Dec 25) 20 (24) 6525-33.
Journal code: O8L. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199304
AB Two abundant high-mobility-group (HMG)-like proteins, HMG B and HMG C, exist in the ciliated protozoan, Tetrahymena thermophila. Of these, HMG C is specific to transcriptionally active macronuclei, while HMG B is found in macronuclei and in transcriptionally inactive ***micronuclei*** [1]. Using Northern and in situ analyses, we show that the genes encoding HMG B and HMG C are not expressed uniformly throughout the vegetative cycle or during the sexual process, conjugation. Elevated expression of both genes is observed during macronuclear S phase of the vegetative cycle
and during endoreplication of developing new macronuclei in later stages of conjugation. Interruption of any of these macronuclear DNA replications
by ***aphidicolin*** leads to a rapid drop in the message levels of HMG B and HMG C. These results resemble what is typically observed for replication-dependent nucleosomal histones and differ from the apparent lack of cell cycle regulation observed for HMG genes in vertebrates. A specific-induction of HMG B mRNA is also observed early in conjugation and
during this interval, inhibition of micronuclear DNA synthesis by ***aphidicolin*** does not affect the message level of HMG B. Thus, during conjugation, expression of HMG B shows both replication-dependent and independent regulation. Results similar to these with HMG B are obtained with histone H4II gene, a gene which is also expressed during micro- and macronuclear S phases during the vegetative cycle. These results demonstrate surprising complexity in the expression of HMG genes in Tetrahymena and lend support to the hypothesis that cell cycle regulation plays an important role in directing HMG-like proteins to the appropriate nucleus [2]. Interestingly, expression of neither HMG gene is perfectly synchronized with that of histone H4II gene during the developmental program suggesting that important differences exist between vegetatively growing (cell cycle control) and conjugating (developmental

control) cells.

L17 ANSWER 47 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1992:385433 BIOSIS
DOCUMENT NUMBER: BR43:52383
TITLE: ***HYDROXYUREA*** -INDUCED LOSS OF EXTRACHROMOSOMALLY AMPLIFIED ONCOGENES IS MEDIATED THROUGH THE FORMATION OF ***MICRONUCLEI*** .
AUTHOR(S): VON HOFF D D; MCGILL J; DAVIDSON K; WAHL G
CORPORATE SOURCE: INST. CANCER RES. CARE, SAN ANTONIO, TEX. 78284, USA.
SOURCE: 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN DIEGO, CALIFORNIA, USA, MAY 20-23, 1992.
PROC
AM ASSOC CANCER RES ANNU MEET, (1992) 33 (0), 359.
CODEN: PAMREA.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L17 ANSWER 48 OF 59 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 92200355 MEDLINE
DOCUMENT NUMBER: 92200355
TITLE: Increased mutagen sensitivity in human cultured fibroblasts
with constitutively high micronucleus levels.
AUTHOR: Rummelein B; Drieschner O; Ehlert U; Weichenthal M; Breitbart E W; Rudiger H W
CORPORATE SOURCE: Unit of Toxicogenetics, University of Hamburg, Germany.
SOURCE: CANCER GENETICS AND CYTOGENETICS, (1992 Feb) 58 (2) 186-90.
Journal code: CMT. ISSN: 0165-4608.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199207
AB The ***induction*** of ***micronuclei*** (MN) by incubation with different mutagenic agents was tested in diploid fibroblast cultures obtained from 15 probands with constitutively high MN rates (15.75-77.25 MN/500 cells; average 36.27 +/- 17.60 MN) and 15 probands (controls) with low MN rates (4-13.75 MN/500 cells; average 8.97 +/- 2.73 MN). In order to
find out whether fibroblast cultures of individuals with increased spontaneous MN levels exhibit an increased sensitivity to various agents with different genotoxic mechanisms, we studied the induction of MN in these cell cultures by ultraviolet (UV) irradiation, mitomycin C (MMC), N-methyl-N-nitro-N-nitrosoguanidine (MNNG) and benzo-(a)pyrene-diol-expoxid (BPDE). In addition, we tested ***aphidicolin*** (APC), a polymerase alpha inhibitor, which is a potent inducer of common fragile sites. Probands with spontaneously high MN showed an significantly increased sensitivity to UV (p less than or equal to 0.005), MMC (p less than or equal to 0.005), and BPDE (p less than or equal to 0.005). No significant differences were found for MNNG and APC as compared to controls.

L17 ANSWER 49 OF 59 MEDLINE DUPLICATE 23
ACCESSION NUMBER: 92174888 MEDLINE
DOCUMENT NUMBER: 92174888
TITLE: ***Coumarin*** inhibits ***micronuclei*** formation

induced by benzo(a)pyrene in male but not female ICR mice.
AUTHOR: Morris D L; Ward J B Jr
CORPORATE SOURCE: Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston 77550.
SOURCE: ENVIRONMENTAL AND MOLECULAR MUTAGENESIS, (1992) 19 (2) 132-8.
Journal code: EMM. ISSN: 0893-6692.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199206
AB ***Coumarin*** has been shown to be an effective inhibitor of carcinogenesis in rodents if given before and during the carcinogen treatment. We investigated the possibility that pretreatment with ***coumarin*** would inhibit the genotoxicity of benzo(a)pyrene (BP) in ICR mice as indicated by the bone marrow micronucleus test, a widely used in vivo test for genotoxicity. Our studies showed that pretreatment of male mice with doses of ***coumarin*** at 65 or 130 mg/kg/day for 1 week (with 1 day of no treatment at midweek) partially inhibited the genotoxicity of BP at a single intraperitoneal dose of 150 mg/kg. Time course experiments showed a decrease in induced ***micronuclei*** in the bone marrow at several time points after the BP treatment, thus indicating a true inhibition and not a lag in the ***induction*** of ***micronuclei*** . However, no inhibition in ***micronuclei*** formation was seen in female mice pretreated with the same doses of ***coumarin*** . ***Coumarin*** treatment alone did not induce ***micronuclei*** in either sex. Future studies are needed to analyze the mechanisms responsible for the difference noted between the sexes.

L17 ANSWER 50 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:628214 CAPLUS
DOCUMENT NUMBER: 117:228214
TITLE: Structural basis of the in vivo ***induction*** of ***micronuclei***
AUTHOR(S): Yang, Wu Lung; Klopman, Gilles; Rosenkranz, Herbert S.
CORPORATE SOURCE: Grad. Sch. Public Health, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Mutat. Res. (1992), 272(2), 111-24
CODEN: MUREAV; ISSN: 0027-5107
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structural basis of the in vivo ***induction*** of ***micronuclei*** was examd. with CASE, a structure-activity relational method. The CASE program identified a no. of structures assocd. with this activity. When used to predict the activity of chems. not included in the learning set, these structural determinants gave a concordance in excess of 83%. The existence of a structural basis for the ***induction*** of ***micronuclei*** will permit an investigation of the mechanistic basis of this phenomenon.

L17 ANSWER 51 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1992:280162 BIOSIS
DOCUMENT NUMBER: BA94:4812

TITLE: CYTOGENOTOXIC EFFECTS OF OCCUPATIONAL EXPOSURE TO N N' METHYLENEBIS-2-AMINO-1 3 4-THIADIAZOLE.
AUTHOR(S): HUANG H; HUANG N; LIN H; GU Z; GU X
CORPORATE SOURCE: DEP. OCCUPATIONAL HEALTH, SCH. PUBLIC HEALTH, SHANGHAI MED.
UNIV., SHANGHAI.
SOURCE: ACTA ACAD MED SHANGHAI, (1992) 19 (1), 57-60.
CODEN: SYDXEE. ISSN: 0257-8131.
FILE SEGMENT: BA; OLD
LANGUAGE: Chinese

AB The study was designed to investigate cytogenotoxic effects of occupational exposure to N,N'-methylene-bis (2-amino-1,3,4-thiadiazole) (MATDA) in 11 workers (2 male, 9 female) exposed to an average level of 0.45 mg/m3 MATDA for 4.apprx.8 years. No significant differences in the incidence of SCE and ***micronuclei*** in peripheral lymphocytes was observed between the exposed group and a control group of 3 male and 11 females. MATDA can damage DNA and induce unscheduled DNA synthesis (UDS) in human lymphocytes in vitro, on a dose-effect relationship. Equal concentrations of ***nicotinamide*** (antagonist of MATDA) added to human lymphocytes culture showed that UDS induced-MATDA could be prevented by ***nicotinamide*** . No evidence of cytogenotoxic effects of occupational exposure were obtained. This might be due to lower levels of exposure in the working population and antagonistic action of ***nicotinamide*** in foodstuff.

L17 ANSWER 52 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89231595 EMBASE
DOCUMENT NUMBER: 1989231595
TITLE: Genotoxicity of 1,4-benzoquinone and 1,4-naphthoquinone in relation to effects on glutathione and NAD(P)H levels in V79 cells.
AUTHOR: Ludewig G.; Dogra S.; Glatt H.
CORPORATE SOURCE: Institute of Toxicology, University of Mainz, D-6500 Mainz,
Germany
SOURCE: Environmental Health Perspectives, (1989) 82/- (223-228).
ISSN: 0091-6765 CODEN: EVHPAZ
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 1,4-Benzoquinone is cytotoxic in V79 Chinese hamster cells and induces gene mutations and ***micronuclei*** . The cell-damaging effects of quinones are usually attributed to thiol depletion, oxidation of NAD(P)H, and redox-cycling involving the formation of semiquinone radicals and reactive oxygen species. To elucidate the role of these mechanisms in the genotoxicity of 1,4-benzoquinone, we measured various genotoxic effects, cytotoxicity, and the levels of glutathione, NADPH, NADH, and their oxidized forms all in the same experiment. 1,4-Naphthoquinone, which does not induce gene mutations in V79 cells, was investigated for comparative reasons. The quinones had a similar effect on the levels of cofactors. Total glutathione was depleted, but levels of oxidized glutathione were slightly increased. The levels of NADPH and NADH were reduced at high concentrations of the quinones with a simultaneous increase in the levels of NADP+ and NAD+. Both compounds induced ***micronuclei*** , but neither increased the frequency of sister chromatid exchange. Only 1,4-benzoquinone induced gene mutations. This effect was observed at low concentrations, where none of the other parameters studied was affected.

When the cells were depleted of glutathione prior to treatment with the quinones, the induction of gene mutations and ***micronuclei*** remained virtually unchanged. We conclude that a) ***induction*** of ***micronuclei*** and glutathione depletion by the two quinones are not linked causally, b) 1,4-benzoquinone induces gene mutations by a mechanism different from oxidative stress and glutathione depletion, and c) glutathione does not fully protect the cells against the genotoxicity of quinones.

L17 ANSWER 53 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 24
ACCESSION NUMBER: 1989:528769 BIOSIS
DOCUMENT NUMBER: BR37:127627
TITLE: ANTIKINETOCHORE ANTIBODIES AND FLOW KARYOTYPING NEW TECHNIQUES TO DETECT ANEUPLOIDY IN MAMMALIAN CELLS INDUCED BY IONIZING RADIATION AND CHEMICALS.
AUTHOR(S): NUESSE M; KRAEMER M; VIAGGI S; BARTSCH A; BONATTI S
CORPORATE SOURCE: GESELLSCHAFT FUER STRAHLEN- UND UMWELTFORSCHUNG, INSTITUT FUER BIOPHYSIKALISCHE STRAHLENFORSCHUNG, PAUL-EHRLICH-STR. 20, 6000 FRANKFURT/M-70, FRG.
SOURCE: FIFTH INTERNATIONAL WORKSHOP ON IN VITRO TOXICOLOGY, SCHLOSS ELMAU, WEST GERMANY, NOVEMBER 1988. MOL TOXICOL, (1987-1988) 1 (4), 393-406.
CODEN: MOTOEX. ISSN: 0883-9492.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L17 ANSWER 54 OF 59 MEDLINE
ACCESSION NUMBER: 89384731 MEDLINE
DOCUMENT NUMBER: 89384731
TITLE: Antikinetochore antibodies and flow karyotyping: new techniques to detect aneuploidy in mammalian cells induced by ionizing radiation and chemicals.
AUTHOR: Nusse M; Kramer M; Viaggi S; Bartsch A; Bonatti S
CORPORATE SOURCE: GSF-Institut fur Biophysikalische Strahlenforschung, Frankfurt am Main, Federal Republic of Germany..
SOURCE: MOLECULAR TOXICOLOGY, (1987-88 Fall) 1 (4) 393-405.
Journal code: NHD. ISSN: 0883-9492.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198912
AB For a possible detection of aneuploidy induction by chemicals and ionizing radiation, fluorescein-bound antikinetochore antibodies (CREST-scleroderma antibodies) were used to discriminate between ***micronuclei*** deriving from acentric fragments or from chromosome loss induced in Chinese hamster cells. The cells were treated with ***aphidicolin*** , adriamycin, Hoechst 33258, colcemid, the alkylating agent diethyl sulfate, and ionizing radiation. The frequency of micronucleated cells, the fraction of kinetochore-positive and -negative ***micronuclei*** per cell, and the fraction of kinetochore-positive ***micronuclei*** was measured using immunofluorescence staining of kinetochores in ***micronuclei*** . Of the ***micronuclei*** and fragmented nuclei induced by colcemid, 99% contained kinetochores, whereas ionizing radiation induced only 4% of kinetochore-positive ***micronuclei*** .

The other drugs induced variable, in some cases also cell-cycle-dependent, fractions of kinetochore positive ***micronuclei*** . With this technique a discrimination between clastogenic effects and effects that occur at the level of spindle formation of the agent studied seems to be possible. Flow karyotyping was used to study the induction of stable homogeneous and numerical aberrations in diploid Chinese hamster cell clones that had survived a dose of 15 Gy gamma-radiation. All analyzed clones showed deviations in their flow karyotypes: the mean number was 9.2 deviations per clone, compared to 1.1 deviations per clone in unirradiated control clones.

L17 ANSWER 55 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1986:219094 CAPLUS
DOCUMENT NUMBER: 104:219094
TITLE: Antimutagenic effects of niacin and analogs of NAD
AUTHOR(S): Lim-Sylianco, Clara Y.; Ko, Elizabeth
CORPORATE SOURCE: Coll. Science, Univ. Philippines, Quezou, Philippines
SOURCE: Nat. Appl. Sci. Bull. (1985), 37(1), 15-24
CODEN: NASBAY; ISSN: 0028-0682
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Well-known mutagens, methylmethanesulfonate [66-27-3], methylcholanthrene [56-49-5], tetracycline [60-54-8], and dimethylnitrosamine [62-75-9], induced the formation of ***micronuclei*** in bone marrow cells of the exptl. mouse, an indication that these mutagens are clastogenic. Niacin [59-67-6] reduced the no. of micronucleated polychromatic erythrocytes induced by methylmethanesulfonate, methylcholanthrene, tetracycline and dimethylnitrosoamine. The best redn. was shown when niacin was administered at the same time as the mutagen. This indicates that niacin exhibits antimutagenic and anticlastogenic properties. Three analogs of NAD were tested for antimutagenic property. These were, ***nicotinamide*** hypoxanthine dinucleotide [1851-07-6], nicotinic acid adenine dinucleotide [6450-77-7], and ***nicotinamide*** guanine dinucleotide [5624-35-1]. Their antimutagenic effects were not statistically different from that of niacin.

L17 ANSWER 56 OF 59 MEDLINE
ACCESSION NUMBER: 84024106 MEDLINE
DOCUMENT NUMBER: 84024106
TITLE: [Synthesis of RNA and DNA in isolated nuclei of Colpoda cucullus (Protozoi Ciliati)].
Sintesi di RNA e DNA nei nuclei isolati di Colpoda cucullus (Protozoi Ciliati).
AUTHOR: Chessa M G; Zoncheddu A; Accomando R; Crippa Franceschi T
SOURCE: BOLLETTINO - SOCIETA ITALIANA BIOLOGIA SPERIMENTALE, (1983 Aug 30) 59 (8) 1142-8.
Journal code: ALS. ISSN: 0037-8771.
PUB. COUNTRY: Italy
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Italian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198402
AB The ciliated protozoan Colpoda cucullus has been cultivated at 27 degrees

C with gentle shaking in a baked lettuce infusion supplemented with Klebsiella suspensions. Under these conditions cells had a mean generation time of about 7 hours and could attain densities up to 20,000/ml and 45,000/ml in the log and stationary phase of growth, respectively. Nuclear preparations obtained from exponentially growing cells by the gum arabic-octanol method showed a satisfactory degree of purity and integrity. They consisted primarily of the large macronuclei attached to which the small ***micronuclei*** were sometimes visible. Upon incubation at 27 degrees C in conventional reaction mixtures nuclear preparations actively incorporated 3H-UTP and 3H-dTTP into acid-insoluble material. alpha-amanitin caused a 50% inhibition of RNA synthesis whereas ***aphidicolin*** did not affect at all DNA synthesis.

L17 ANSWER 57 OF 59 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 83192229 MEDLINE
DOCUMENT NUMBER: 83192229
TITLE: ***Induction*** of ***micronuclei*** in the mouse. Revised timing of the final stage of erythropoiesis.
AUTHOR: Hart J W; Hartley-Asp B
SOURCE: MUTATION RESEARCH, (1983 May) 120 (2-3) 127-32. Journal code: NNA. ISSN: 0027-5107.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 198308
AB The early effects of X-rays, vincristine, cyclophosphamide, quinacrine dihydrochloride, cycloheximide, actinomycin D and ***hydroxyurea*** on the ***induction*** of ***micronuclei*** in mouse bone-marrow erythrocytes were studied. A significant increase in the incidence of ***micronuclei*** in polychromatic erythrocytes was seen as early as 5 h after a single treatment with vincristine, 6 h after treatment with X-rays and 10 h after treatment with cyclophosphamide. The cell kinetics of the mouse erythropoietic system described by Cole et al. (1981) can be modified to fit these results. According to this revised model, the final mitosis takes place only 5 h before the expulsion of the nucleus.

L17 ANSWER 58 OF 59 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 83051257 EMBASE
DOCUMENT NUMBER: 1983051257
TITLE: [Micronucleus-induction test on Allium sativum for differentiation between clastogens and spindle poisons]. UN 'TEST D'INDUCTION DE MICRONOYAU' SUR ALLIUM SATIVUM; DIFFERENTIATION DE SUBSTANCES CLASTOGENES ET MITOCLASIQUES.
AUTHOR: Valadaud Barrieu D.
CORPORATE SOURCE: Dep. Rech. Seita, 75340 Paris Cedex 07, France
SOURCE: Mutation Research, (1983) 119/1 (55-58). CODEN: MUREAV
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
022 Human Genetics
LANGUAGE: French
SUMMARY LANGUAGE: English

AB A rapid and simple test was developed on root tips of Allium sativum. A comparison of diameters of ***micronuclei*** induced by clastogens and by spindle poisons has permitted a differentiation of the two types of substance.

L17 ANSWER 59 OF 59 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1968:38397 CAPLUS
DOCUMENT NUMBER: 68:38397
TITLE: Characteristics of the antimitotic activity of ***hydroxyurea*** and hydroxylamine evaluated with the Allium test
AUTHOR(S): Truhaut, Rene; Deysson, Guy; Bradel, Yvonne
CORPORATE SOURCE: Fac. Pharm. Paris, Paris, Fr.
SOURCE: C. R. Hebd. Seances Acad. Sci., Ser. D (1967), 265(22), 1756-9
CODEN: CHDDAT
DOCUMENT TYPE: Journal
LANGUAGE: French
AB Treatment of Allium roots with ***hydroxyurea*** (5 .times. 10-8 mole/ml.) caused the appearance of ***micronuclei*** . A 10-7 mole/ml. concn. did not reduce the mitotic activity, but caused chromosomal fragmentations after a 3-day treatment. A 5 .times. 10-7 mole/ml. concn. was highly mitodepressive, causing chromosomal fragmentations after a 3-hr. incubation and a depression of the mitotic index after a 24-hr. incubation. This concn. also caused the appearance of chromosomal fragmentations in the occasional mitosis present, and of ***micronuclei*** . The effects of a 24-hr. treatment were reversible when the roots were placed in half-strength Knop medium for 48 hrs. Hydroxylamine-HCl (5 .times. 10-8 and 10-7 mole/ml.) caused only a temporary mitodepression, although a 5 .times. 10-7 mole/ml. concn. caused the complete disappearance of mitosis after a 24-hr. treatment. A 3-day incubation at a 5 .times. 10-7 mole/ml. concn., a 48-hr. incubation at a 10-6 mole/ml. concn., and a 24-hr. incubation at a 10-5 mole/ml. concn. had lethal effects. The activity of hydroxylamine-HCl was reversible only after a 3-hr. incubation at 10-6 and 10-5 mole/ml. concns. The appearance of binucleate cells was the only mitotic anomaly caused by hydroxylamine-HCl (at a 10-7 mole/ml. concn.); extremely infrequent ***micronuclei*** were found in meristems treated with a 10-5 mole/ml. concn. Chromosomal fragmentations were therefore only formed after a short treatment at a high, rapidly lethal concn. (10-5 mole/ml.). The antimitotic activity of ***hydroxyurea*** is apparently not caused through an in vivo transformation of this compd. to hydroxylamine.